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No. 10-972

Supreme Court, U.S.
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IN THE
Supreme Court of the United States

ELI LILLY AND COMPANY,

Petitioner,

v.

SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Whether the Federal Circuit improperly transformed the doctrine of "double patenting," in conflict with a "vast body of precedent" cited by four dissenting judges, by creating a new bright-line rule that invalidates a subsequent patent on a nonobvious, newly discovered use of a basic invention solely because it was disclosed, but not claimed, in the final text of the earlier basic patent.

PARTIES TO THE PROCEEDING

The parties are petitioner Eli Lilly and Company ("Lilly") and respondent Sun Pharmaceutical Industries, Ltd. ("Sun").

RULE 29.6 STATEMENT

Lilly has no parent corporation, and no publicly held company owns 10 percent or more of Lilly stock.

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OPINIONS

The opinion of the court of appeals (Pet. App. 1a-18a) is reported at 611 F.3d 1381 (Fed. Cir. 2010). The denial of rehearing and rehearing en banc, over a four-judge dissent (Pet. App. 129a-41a), is reported at 625 F.3d 719 (Fed. Cir. 2010). The opinion of the district court (Pet. App. 19a-33a) is reported at 647 F. Supp. 2d 820 (E.D. Mich. 2009). (The opinion of another district court holding the patent claims at issue nonobvious, Pet. App. 34a-128a, is reported at *Eli Lilly and Co. v. Sicor Pharmaceuticals, Inc.*, 705 F. Supp. 2d 971 (S.D. Ind. 2010).)

JURISDICTION

The court of appeals entered its judgment on July 28, 2010, and denied a petition for rehearing and rehearing en banc on November 1, 2010. The court of appeals had jurisdiction under 28 U.S.C. § 1295(a)(1). This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS

35 U.S.C. § 100(b) provides: "When used in this title unless the context otherwise indicates— *** The term 'process' means process, art, or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material."

35 U.S.C. § 101 provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new

and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

STATEMENT OF THE CASE

I. INTRODUCTION

This Court should address the conflict between the decision below and decades of precedents that prompted four judges of the Federal Circuit to dissent from that court's refusal to rehear this case en banc. This Court has not spoken on the largely judge-made doctrine of "double patenting" since before enactment of the 1952 Patent Act. Left to its own devices, the Federal Circuit has now cut that doctrine free from its jurisprudential moorings and transformed it in a way that conflicts with binding precedent, the patent statute, and the limited reasons for the doctrine's existence. Review is needed to set the doctrine right and prevent the harm caused by the sudden distortion of this once stable area of law.

The double-patenting doctrine is an elaboration of the basic statutory command that an inventor is entitled to "a patent"—not more than one patent—for any "new and useful" invention. 35 U.S.C. § 101. The aspect of the doctrine at issue here, "obviousness-type double patenting," extends the principle to bar the issuance of two patents claiming obvious variations of the same invention. That bar serves a gap-filling role in the statute, where the statute's nonobviousness provision, 35

U.S.C. § 103, does not already apply to prevent this result.

"Obviousness-type double patenting" has long required, as its essential precondition, a determination that the second claimed invention would have been obvious from the first claimed invention. Now, however, a deeply divided Federal Circuit has let stand a panel opinion that fundamentally departs from that doctrine's limited prohibition on twice *claiming* the same invention, or obvious variants, and instead finds double patenting based solely on *disclosure* of the second invention in the text of the first patent. Specifically, the panel held that when a chemical composition has been patented, the doctrine legally bars the separate patenting of *any* use for it that was *disclosed* in the text of the composition patent, no matter how nonobvious from the composition invention and how much later its discovery.

According to the Federal Circuit panel, it does not matter that the use (1) was "a new use of a known *** composition of matter" as expressly made patentable by 35 U.S.C. § 100(b), (2) was discovered well after the invention of the compound, (3) was added by amendment to the text of the composition patent long after its original filing date, and (4) was completely nonobvious from the compound and its originally discovered and disclosed use. Indeed, the patent-defeating sin found to have been committed here was *disclosing* the otherwise separately patentable new use in what became the final text of the issued compound patent. That the new-use

invention here would have been patentable had it been *concealed* from readers of the composition patent confirms that the new bright-line rule is contrary to the fundamental patent policy of encouraging disclosure.

This new rule is in conflict with this Court's decision in *Miller v. Eagle Manufacturing Co.*, 151 U.S. 186 (1894). There, this Court explained that simple *disclosure* of an improvement invention in the text of an earlier patent claiming a basic invention is not a bar to issuance of a separate patent on the disclosed but unclaimed invention. *Id.* at 198. *Miller* and decades of ensuing lower court decisions prohibit issuance of a second patent only when the subject matter of the subsequent patent's claims would have been obvious from the earlier *claimed* invention. The Federal Circuit's new rule dispenses with that inquiry.

The circumstances of this case make the error in the Federal Circuit's transformation of the doctrine particularly clear. Here, the originally claimed compound invention was actually statutory prior art to the later new-use invention, so the normal statutory obviousness provision (section 103) directly applied. That eliminated any need for a gap-filling double patenting doctrine. And, in fact, a full trial in a related action resulted in an adjudication that the new use was *not* obvious from the earlier-patented composition and its originally discovered use. Nevertheless, the Federal Circuit here crafted a new judge-made rule to negate the result mandated by the applicable statutory test.

Four dissenting Federal Circuit judges recognized that this unwarranted transformation of the double patenting doctrine "violates a vast body of precedent." Pet. App. 138a. According to the dissenters, the court's 5-to-4 vote refusing to rehear the case en banc to resolve this conflict constituted "an indictment of the ability of [that] court to provide stable law in the areas entrusted to [it]." *Id.* at 141a. As the Federal Circuit has exclusive jurisdiction over appeals in cases arising under the patent laws, only this Court can act to correct this fundamental change of law, which upsets the legitimate expectations of patent holders, discourages investment in the exploration of new uses for basic inventions, and eviscerates substantial long-term investments made in reliance on hitherto well-settled legal principles.

II. BACKGROUND

A. "New Use" Inventions and the Statutory Scheme for Their Protection

A significant amount of important pharmaceutical development focuses on discovering medically important new uses for known chemical compositions. These new uses are often entirely nonobvious. *See, e.g., Eli Lilly and Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010) (old cancer drug developed for osteoporosis); *Eli Lilly and Co. v. Actavis Elizabeth LLC*, No. 07-CV-3770, 2010 WL 3210516 (D.N.J. Aug. 12, 2010) (old antidepressant drug developed for ADHD); *Glaxo Grp. Ltd. v. Teva Pharms. USA, Inc.*, No. 02-219-

GMS, 2004 WL 1875017 (D. Del. Aug. 20, 2004) (old migraine drug developed for nausea and emesis).

To develop products for such new uses, and establish the necessary safety and efficacy, a pharmaceutical company must engage in lengthy, expensive, and uncertain testing. Without the prospect of patent protection on the nonobvious new use, these massive and risky investments would not be made, and the beneficial medicines would not be developed.

The patent statute recognizes the importance of new uses of known compositions. In 1952, Congress enacted 35 U.S.C. § 100(b) to confirm the patentability of such inventions. Section 100(b) expressly states that new uses of known compositions are among the "processes" qualifying for patents under section 101, subject of course to the other requirements of the statute, most notably the requirement of section 103 that the new-use invention have been nonobvious. This statutory scheme makes clear that a chemical composition and a later-discovered nonobvious new use for it are *different* patentable inventions.

The statutory scheme thus contemplates a familiar pattern. The inventor of a new, nonobvious composition may obtain a patent once he has identified both the composition and a utility for it. Until a first use is discovered, there is no invention. *Brenner v. Manson*, 383 U.S. 519, 528-29 (1966). The patent on the composition broadly entitles him to exclude others from using that composition for any and all purposes, even subsequently discovered

nonobvious uses. 35 U.S.C. § 271(a) (any "use" of a patented composition is an infringing act). Nevertheless, the subsequent discoverer of a nonobvious "new use" for that composition, though unable to use the new discovery without infringing the composition patent, is entitled to obtain a separate patent for that new use. 35 U.S.C. § 100(b). That patent narrowly excludes others only from the claimed newly discovered use, not any other use of the composition. Importantly, nothing in the statute disqualifies the inventor of the old composition (out of all such potential improvers) from searching for and patenting nonobvious new uses of it, or requires the inventor to claim all of his separately patentable inventions in a single patent. *See, e.g., O'Reilly v. Morse*, 56 U.S. 62, 122 (1853).

In this common situation, the basic composition patent is said to "dominate" the later improvement patent. Such inevitable "domination," however, does not give rise to "double patenting." As the Federal Circuit long ago observed, it is improper to "confuse[ ] double patenting with 'domination' which, by itself, does not give rise to 'double patenting' ***." *In re Kaplan*, 789 F.2d 1574, 1577 (Fed. Cir. 1986).

Under longstanding law, obviousness-type double patenting occurs only when the invention *claimed* in a later patent is an obvious variant of the invention *claimed* in an earlier patent. In this regard, it is the patent *claims* that define what has been patented. 35 U.S.C. § 112, ¶ 2. The patent specification, in contrast, in teaching how to make

and use the invention (35 U.S.C. § 112, ¶ 1), may disclose all sorts of unclaimed material. Double patenting, therefore, has always focused on the invention *claimed*, not on what has been disclosed but not claimed, since the *claims* define what has been allegedly twice "patented."[1]

B. The Lilly Inventions

This litigation concerns Lilly's "gemcitabine" anticancer product, Gemzar®, which has become the standard of care for treating pancreatic cancer. C.A.J.A. 162-63, ¶ 49.[2] Two patents relating to Gemzar® are at issue—Lilly's U.S. Patent No. 4,808,614 ("the '614 patent"), claiming both the chemical compound gemcitabine and its originally discovered antiviral use (C.A.J.A. 156, claims 12-13), and U.S. Patent No. 5,464,826 ("the '826 patent"), claiming a later-discovered process of using gemcitabine to treat cancer (*id.* at 25, claims 2, 7). *See also* Pet. App. 3a-5a. These patents claim two different inventions, one discovered after the other, and each independently worthy of patent protection.

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[1] The Federal Circuit's predecessor long ago held that the double-patenting doctrine also applies when two patents are commonly owned from the outset, even if (like Lilly's two patents here) they name different inventors. *In re Keim*, 229 F.2d 466, 469 (CCPA 1956).

[2] "C.A.J.A." refers to the Joint Appendix in the court of appeals.

1. The Invention of Gemcitabine and Its Antiviral Activity

Working in a pharmaceutical field where both the synthesis and biological properties of compounds were highly unpredictable, Dr. Larry Hertel, a Lilly scientist, proposed the synthesis of chemical compounds called "difluoronucleosides" with the hope that such compounds would have more *antiviral* activity than previously existing compounds. C.A.J.A. 173-74.[3] Dr. Hertel was the first person who successfully made such compounds (*id.* at 176-77, 180), and, on March 10, 1983, Lilly filed the original patent application describing and claiming Dr. Hertel's difluoronucleoside invention (*id.* at 187-228). That original application contained a complete and enabling disclosure of gemcitabine, how to make it, and how to use it as an antiviral agent. The inventions directed to gemcitabine and how to use it as an antiviral agent were ultimately claimed in the '614 patent. *Id.* at 156, claims 12-13. The original application did *not* describe the as-yet undiscovered anticancer use of gemcitabine. Pet. App. 3a.

2. The Subsequent Discovery of Gemcitabine's Anticancer Use

Eight months after filing his original patent application, Dr. Hertel submitted gemcitabine to

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[3] The factual background underlying this case, deemed irrelevant by the Federal Circuit, is described in full in the Indiana district court's opinion reprinted at Pet. App. 57a-68a.

another Lilly scientist, Dr. Gerald Grindey, for testing as a potential anticancer agent. C.A.J.A. 232. Gemcitabine exhibited surprising and unprecedented activity against a wide array of solid tumors. *Id.* at 247-48, 250. This activity was "a very unusual feature," as no similar compound was previously known to exhibit this type of broad spectrum activity. *Id.* at 248.

As a result of this new anticancer discovery, Lilly filed a *new* patent application on December 4, 1984, which named Drs. Grindey and Hertel as joint inventors and described and claimed, *inter alia*, the process of using gemcitabine to treat cancer, as permitted by 35 U.S.C. § 100(b). Pet. App. 4a-5a; C.A.J.A. 13. This new application, which ultimately led to issuance of the '826 patent, contained extensive *in vitro* and *in vivo* experimental data supporting the method of using gemcitabine to treat cancers in mammals. C.A.J.A. 140-42.

C. Procurement of the '614 and '826 Patents

On the day Lilly filed the application that ultimately issued as the '826 patent, it also amended the text of Dr. Hertel's original (and still-pending) application by filing a so-called "continuation-in-part" ("CIP") application. Pet. App. 3a. To ensure satisfaction of any possible obligation under the "best mode" requirement of the patent statute, Lilly included *one paragraph* in the CIP application that briefly disclosed the newly discovered anticancer use

of gemcitabine. *Id.* at 3a-4a; C.A.J.A. 154, col. 17, lines 53-68.[4] The paragraph informing the public of this newly discovered use for gemcitabine did not include the extensive supporting data found in the '826 patent, and the amended application did not claim, *i.e.*, seek to patent, this new use. Pet. App. 3a-4a.

To qualify for patent protection, an invention must be "useful." 35 U.S.C. §§ 101, 112 ¶ 1. During the prosecution of the applications leading to the '614 patent, the U.S. Patent and Trademark Office (PTO) repeatedly noted that the added use of gemcitabine as a treatment for cancer was *not* the utility supporting the pending compound claims. C.A.J.A. 262, 266-67. In response, Lilly agreed, stating that "[t]he Examiner correctly notes that the Applicant is not relying on such data to support the utility of the claimed invention[;] Applicant simply supplies such data to meet the best mode requirement of the statute." *Id.* at 273, 278-79.

Thus, the issued '614 patent contains the paragraph that was added in 1984 to mention the

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[4] Under the "best mode" requirement of 35 U.S.C. § 112, ¶ 1, a patentee must disclose the best way it knows of making and using the claimed invention, even if that best mode was not his invention claimed in that patent. *See Kaplan*, 789 F.2d at 1575. In 1984, the law was unclear whether the best mode needed to be updated when filing a continuation application. It is now clear that updating was not required. *Transco Prods. Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 558 (Fed. Cir. 1994).

anticancer use of gemcitabine but does not *claim* the process of treating cancer discovered later by Drs. Grindey and Hertel (together). Instead, claim 12 of the '614 patent (with Dr. Hertel as the sole inventor) recites the compound gemcitabine, and claim 13 recites methods of using gemcitabine to treat viral infections, as fully disclosed in the original 1983 application. *Id.* at 156; Pet. App. 4a.

In contrast, the '826 patent, with Drs. Grindey and Hertel named as joint inventors, recites (in claims 2 and 7) processes of using gemcitabine to treat cancer. C.A.J.A. 25; Pet. App. 4a-5a. In issuing the '826 patent, the PTO cited and considered the '614 patent and found the later-discovered anticancer use to have been nonobvious and separately patentable from Dr. Hertel's earlier invention of gemcitabine and its antiviral use. *See* C.A.J.A. 13.

D. The Michigan District Court Decision

Lilly sued respondent Sun in the Southern District of Indiana for infringing the '614 and '826 patents, having already sued Sicor Pharmaceuticals, Inc. ("Sicor") there on the same patents. Sun denied personal jurisdiction, leading to dismissal of the Indiana suit against Sun, and then brought this declaratory-judgment action against Lilly in Michigan. The Michigan district court refused to transfer the action to Indiana, creating parallel cases in two separate district courts.

It is undisputed (in both cases) that the '614 patent *claims* were entitled to the benefit of their

original 1983 filing date and that the corresponding disclosure in the '614 patent was, therefore, prior art to the '826 patent available for a section 103 obviousness analysis. Pet. App. 3a n.1, 106a n.38.[5] Sun nonetheless initially moved for summary judgment that the '826 patent was invalid under the judge-made doctrine of "obviousness-type" double patenting. In that motion, Sun, relying on *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003), argued that Lilly could not patent the anticancer use of gemcitabine because the amended text of the '614 patent mentioned (though did not claim) the later-discovered anticancer use.

The district court, reading *Geneva* as Sun urged, granted Sun's motion, invalidated the '826 patent, and entered judgment under Fed. R. Civ. P. 54(b). Pet. App. at 5a-6a, 31a-33a. As explained more fully below, *see* pp. 24-26, *infra*, this was

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[5] Because the '614 patent claimed only subject matter that was fully disclosed in the original 1983 application, 35 U.S.C. § 120 mandated that it be treated as if filed on that original 1983 date, with respect to that original disclosure. *See* Pet. App. 70a-71a. Thus, the original disclosure and issued claims were "prior art" under 35 U.S.C. § 102(e)—and hence under 35 U.S.C § 103—against the subsequent anticancer invention discovered by "another," *i.e.*, Drs. Grindey and Hertel jointly. *See In re Wertheim*, 646 F.2d 527, 537-39 (CCPA 1981). Only the disclosure that was in the original application and carried forward into the issued patent, and not the later-added mention of the anticancer use, qualified as prior art as of the 1983 filing date. *See In re Lund*, 376 F.2d 982, 988 (CCPA 1967).

incorrect as *Geneva* addressed only a special situation, not present here, where the evidence showed that the separate patents claimed aspects of a *single* patentable invention (a compound and the sole originally disclosed use for it needed to make the compound eligible for patent protection under *Brenner*).

E. The Indiana District Court Decision

Before the Michigan district court entered its Rule 54(b) judgment, the Indiana district court held a trial in the earlier-filed suit against Sicor to address the validity of both the '614 and the '826 patents. Pet. App. 34a-128a. As in Michigan, it was undisputed that the disclosure of gemcitabine and its antiviral use in the '614 patent was prior art to the '826 patent for section 103 purposes. *Id.* at 70a-72a, 106a n.38. After a trial producing a fully developed record, the court held that the anticancer use claimed in the '826 patent (claims 2 and 7) would *not* have been obvious under section 103 from the disclosure of gemcitabine and its antiviral use in the '614 patent. *Id.* at 105a-20a. Notwithstanding its nonobviousness conclusion, the Indiana court ruled against Lilly because it deemed itself bound to give issue-preclusive effect to the Michigan decision, which was made final after the Indiana trial ended

but before the Indiana court ruled. *Id.* at 72a-75a & n.26, 123a.[6]

F. The Federal Circuit Panel Opinion

A three-judge panel of the Federal Circuit affirmed the invalidity judgment of the Michigan court, holding that the obviousness-type double patenting doctrine prevented Lilly from separately patenting its later-discovered process for treating cancer using the previously patented gemcitabine compound. Based on its reading of *Geneva*, the panel held that a later patent is necessarily invalid for double patenting whenever "an earlier patent claim[s] a compound, disclosing its utility in the specification, and [the] later patent claim[s] a method of using the compound for a use described in the specification of the earlier patent." *Id.* at 8a.

Thus, even though "double patenting" is concerned only with the inventions *claimed*, the panel expanded the doctrine to rest invalidity merely on what was *disclosed* in the final text of the earlier patent. According to the panel, it is *irrelevant* for purposes of its bright-line rule when or why the additional utility disclosure was added to the earlier patent, whether the utility was a subsequent invention, whether that utility was claimed, or whether that utility would have been obvious from the earlier patent's claimed invention. The Federal

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[6] Lilly submitted this decision to the Federal Circuit during the pendency of the appeal in the present case as supplemental authority.

Circuit conspicuously did not hold, because at least section 100(b) forbids it, that the new use of the known gemcitabine compound discovered jointly by Drs. Grindey and Hertel was the same invention as the compound itself and its original antiviral use discovered entirely by Dr. Hertel alone and claimed in the '614 patent.

G. The Split Over En Banc Review

The Federal Circuit denied Lilly's petition for rehearing en banc on November 1, 2010, by a vote of 5-to-4. *Id.* at 129a-32a.

Judge Newman, joined in dissent by Chief Judge Rader, Judge Lourie, and Judge Linn, explained that the panel had radically altered the longstanding law of double-patenting. *Id.* at 134a-41a. The four dissenters wrote: "[t]he specifications of the patents are irrelevant to the double patenting analysis, other than to guide in construing the claims," and "[t]o determine whether there is double patenting it is the claims that are compared." *Id.* at 135a. The dissenting judges declared: "*The law of double patenting is contrary to the panel's holding[,]*" and "*[t]he panel opinion violates a vast body of precedent.*" *Id.* at 136a, 138a (emphasis added). Notably, the dissenters included Chief Judge Rader, the author of the Federal Circuit's opinion in *Geneva* upon which the panel relied. As the dissent noted, "[t]he panel apparently was misdirected by an overly-broad statement in *Geneva*." *Id.* at 138a.

In addition to pointing out the serious legal error in the panel's decision, the dissenting judges

also criticized the Federal Circuit for not rehearing the case en banc. *Id.* at 134a-35a, 141a. Because the panel opinion conflicts with numerous precedents, and earlier precedent is supposed to control unless overruled en banc,[7] the Federal Circuit's refusal to resolve the conflict was said to constitute "*an indictment of the ability of [the] court to provide stable law in the areas entrusted to [it].*" *Id.* at 141a (emphasis added). Thus, the denial of rehearing en banc, "leaves the innovation community without guidance" on which to rely. *Id.*

REASONS FOR GRANTING THE PETITION

As the four-judge dissent from denial of en banc review explains, the panel here abandoned the longstanding approach to "double patenting" to unmoor it from its foundation—in the statute and this Court's and lower courts' precedents—in simply protecting against securing duplicative *claims* for the same invention or obvious variants. Departing from the fundamental purpose of the "double patenting" doctrine, the decision below creates a new bright-line rule that invalidates a second patent's claim to what is *not* the same as or an obvious variant of a previously claimed invention, improperly relying on what was merely *disclosed* in the final text of the first patent. This new rule upsets the reliance interests of researchers

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[7] The Federal Circuit follows the rule that one panel cannot overrule another panel. In the case of conflict between its panel opinions, the earlier opinion controls. *Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988).

conducting uncertain and costly investigations of new uses of already known chemical compounds, indeed, new uses of any basic invention. This Court, which has not addressed double patenting since the 1952 Act took effect, should review the Federal Circuit's ruling and set the doctrine back on its historic footing.

I. The Federal Circuit's Transformation of the Double-Patenting Doctrine Cannot Be Reconciled with Precedent

A. The Panel's Decision Violates a Century of Double-Patenting Precedent

Consistent with its source in sections 101 and 100(b), the judge-made rule of double patenting has until now not prevented the patenting of nonobvious improvement inventions. Instead, it has merely prevented two patents from issuing on the same or an obvious variation of the same invention. There being no allegation that the *same* invention has been twice claimed here, this case deals with "obviousness-type double patenting," as the panel below expressly acknowledged. Under that doctrine, a century of binding precedent precluded its application without a determination that the subject matter of the later claims would have been obvious from the earlier claimed invention. The Federal Circuit, however, has now contradicted that precedent, dispensing with the required obviousness analysis and substituting a new bright-line test that invalidates a later patent based entirely on an unclaimed disclosure in the earlier patent.

1. The New Rule Conflicts with This Court's Precedent

More than a century ago, in *Miller*, 151 U.S. at 198, this Court addressed the distinction between improperly patenting the same invention twice, *i.e.*, double patenting, and permissibly patenting a nonobvious improvement of an existing invention. The Court explained that it was permissible to patent improvements of prior inventions: "It is settled *** that an inventor may make a new improvement on his own invention of a *patentable character*, for which he may obtain a separate patent *** where the [later-patented] invention is clearly distinct from, and independent of, one previously granted." *Id.* at 199 (emphasis added).

In so holding, the Court made abundantly clear that *disclosure* of the subsequent improvement in the text of the earlier patent was *not* a bar to separate patentability. This Court stated: "where the second patent covers matter *described in the prior patent*, essentially distinct and separable from the invention covered thereby, and claims made thereunder, its validity *may be sustained*." *Id.* at 198 (emphasis added). Thus, matter, even though described in a prior patent, may be separately patented by the inventor as long as it is "distinct and separable" from the invention claimed in the prior patent.

In *Miller*, this Court also endorsed use of the obviousness standard to assess alleged double patenting by using the words "patentable novelty" to describe a distinct invention. *Id.* at 200. Those

words are today recognized as a synonym for the nonobviousness standard embodied in section 103 since 1952. *See* H.R. Rep. 82-1923, at 18 (1952) (Revision Note explaining that section 103 addresses "patentable novelty" or "invention"), quoted in *Graham v. John Deere Co.*, 383 U.S. 1, 16 n.8 (1966); P.J. Federico, *Commentary on the New Patent Act*, reproduced at 75 J. Pat. & Trademark Off. Soc'y 161, 180 (1993) ("Patentable novelty or invention (section 103)").

In short, this Court's own precedent made clear—more than 100 years ago—that even if subject matter is *described* in a prior patent, that subject matter is still separately patentable if it is nonobvious in view of the invention previously claimed. The panel's new bright-line test contradicts *Miller* by finding obviousness-type double patenting based solely on what was described in the text of the earlier patent without *any* consideration of whether the later-claimed invention was nonobvious in view of the invention claimed in the first patent.

2. The New Rule Conflicts with Decades of Other Binding Precedent

Consistent with this Court's holding in *Miller*, the dissenting Federal Circuit judges explained that decades of judicial decisions in the courts of appeals required that double patenting be assessed by comparing the claimed subject matter to determine if the later claims define a nonobvious patentable invention in view of the earlier-claimed invention. Pet. App. 135a-38a. Under numerous precedents,

including of the Federal Circuit itself and its predecessor,[8] it was not enough to examine the prior specification, as was done by the panel here, to see if the text refers to the improvement invention later claimed. *Id.* at 136a-38a.

For example, in the Federal Circuit's own *Kaplan* case, the earlier-issued patent contained a claim for a method of making certain chemical compounds in the presence of an organic solvent. 789 F.2d at 1575. Kaplan was listed as the sole inventor of the earlier patent. *Id.* at 1574. The specification of the Kaplan patent disclosed many examples of different solvents that could be used in the method, but example 45 disclosed a specific mixture of two solvents. *Id.* at 1575. That mixture was the subsequent joint invention of Kaplan and another inventor, Walker, and was thus *not* claimed in the Kaplan patent. *Id.* It was, however, disclosed in the specification because "it was part of the 'best mode' of practicing" the invention. *Id.*

Kaplan and Walker later filed a joint patent application that contained a single claim specifically directed to an "improvement" of the earlier Kaplan process by carrying out the prior method with this particular solvent mixture. *Id.* Improperly confusing "domination" with "double patenting," the PTO rejected the claim on the grounds of double

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[8] The Federal Circuit adopted precedent from the U S. Court of Customs and Patent Appeals (CCPA) as binding on it in *South Corp. v. United States*, 690 F.2d 1368, 1369 (Fed Cir. 1982).

patenting because "both claims embrace[d] the same subject matter." *Id.* at 1576-77.

The Federal Circuit *reversed*, even though the later-claimed mixed solvent was *expressly described* in the specification of the earlier-filed patent. *Id.* at 1580-81. The court explained that double patenting must be assessed by examining the claimed subject matter and assessing whether such subject matter is nonobviousness in view of the prior claims. *Id.* at 1580. The facts of *Kaplan* parallel the present case. Yet the panel in this case made the same errors of law previously corrected in *Kaplan*.

Like *Kaplan*, other Federal Circuit decisions insisted that only the invention claimed in the earlier patent, not anything else that might be in the disclosure, determined whether a second patent constituted double patenting. *See Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1277 (Fed. Cir. 1992) (holding that double patenting "is altogether a matter of what is claimed"); *Amgen Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009) (holding that in assessing double patenting, the patent disclosure is not prior art).

The same is true for the binding precedent from the CCPA. The required analysis is illustrated by *In re Sebek*, 347 F.2d 632 (CCPA 1965), where the court rejected an analysis that examined merely whether the later claimed subject matter had been described in the specification of a prior patent. *Id.* at 634 n.4. Instead, the CCPA, as required by *Miller*, considered whether the later-claimed subject matter would have been *obvious* in view of the invention

previously *claimed*. *Id.* at 636. Only after conducting that analysis did the *Sebek* court find obviousness-type double patenting (because one skilled in the art, having the earlier-claimed steroid and the knowledge in the art about anti-inflammatory effects of structurally related steroidal compounds, would have found the later-claimed anti-inflammatory use of the earlier-claimed steroidal compound obvious). *Id.*[9]

As the Federal Circuit dissenters noted (Pet. App. 137a-38a), the CCPA repeatedly required such a claim-to-claim analysis in order to assess double patenting. *In re Vogel*, 422 F.2d 438, 441 (CCPA 1970); *In re Plank*, 399 F.2d 241, 242 (CCPA 1968); *In re Aldrich*, 398 F.2d 855, 859 (CCPA 1968); *In re Boylan*, 392 F.2d 1017, 1018 n.1 (CCPA 1968); *In re Braithwaite*, 379 F.2d 594, 600 n.4 (CCPA 1967); *In re Borah*, 354 F.2d 1009, 1018 (CCPA 1966); *In re Sutherland*, 347 F.2d 1009, 1015 (CCPA 1965); *In re Sarett*, 327 F.2d 1005, 1013 (CCPA 1964). "[T]he issue of obviousness-type double patenting is directed to whether the invention claimed in a later patent is an obvious variant of the invention claimed in an earlier patent." Pet. App. 138a. Yet just such

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[9] *See also Keim*, 229 F.2d at 469-70 (holding that method of using emulsions to size paper would not have been obvious in view of prior patent that claimed emulsions, even though same use had been described in the prior patent), *In re Maxwell*, 188 F.2d 479, 484-85 (CCPA 1951) (holding method of using colloid to maintain strength of paper was a distinct invention from the colloid itself, even though prior patent claimed colloid and described the same use of the colloid later claimed)

an analysis was rejected by the Federal Circuit as legally irrelevant in this case—and, indeed, was not and could not have been performed on summary judgment, where (in order to avoid genuine factual disputes) the courts had to *assume* that the anticancer use was not obvious from the compound and its antiviral use.

B. The Panel's New Rule Is Unprecedented

In opposition to all of the above authority, including this Court's decision in *Miller*, the panel relied on a misreading of *Geneva*, 349 F.3d at 1385-86. Even if *Geneva* had articulated the present panel's bright-line rule, the rule would still warrant review as inconsistent with *Miller* and all the other precedents noted. But *Geneva* did not in fact announce or apply the panel's rule. Indeed, as noted above, now-Chief Judge Rader, who wrote the opinion in *Geneva*, *dissented* from the newly created bright-line rule in the present case.

Geneva involved a compound with a *single* known utility. *Id.* at 1385-86. That lone utility was disclosed in the original application, was necessary for the compound to be "useful," as required by section 101, and thus was essential to make the compound eligible for patent protection. *See id.* As this Court held in *Brenner*, 383 U.S. at 528-29, a compound is not a patentable invention until a use for it is identified. On its facts, *Geneva* concluded that there was but a single invention—the compound with its sole disclosed use—because the discovery of that use was what turned the discovery of the

compound into a patentable invention in the first place. *See Geneva*, 349 F.3d at 1386. The sole disclosed use and the compound, therefore, were merely aspects of the *same invention* (necessarily by the same inventive entity) and could not be claimed in separate patents. *See id.* at 1385-86. For that reason, *Geneva* did not even have to rely on "obviousness-type" double patenting.

The panel in this case misread *Geneva*, taking language out of context and applying it to a radically different situation. Here, the invention of gemcitabine and its antiviral use was complete well *before* the method of using gemcitabine to treat cancer was discovered. *See* pp. 9-10, *supra*. Indeed, the later-discovered anticancer use (claimed in Lilly's '826 patent) was discovered by a *different* inventive entity after the patent application on Dr. Hertel's invention of gemcitabine and its antiviral use had been filed. *Id.* at 9-12. The later-discovered anti-cancer use *cannot*, therefore, be part of the same invention, unlike in *Geneva*. Here, an obviousness analysis comparing the later-claimed invention to the earlier-claimed invention *is* required. Yet the Federal Circuit dispensed with any such analysis and found double patenting even assuming (as it must on summary judgment) that the anticancer use was *not* obvious from the previously claimed invention of the compound and its antiviral use. That a court might find after trial on the merits that the anticancer use was actually nonobvious, as the Indiana court did, was simply immaterial.

The panel here relied heavily on a sentence from a 1931 CCPA decision, *In re Byck*, 48 F.2d 665, 666 (CCPA 1931), that *Geneva* had quoted:

> It would shock one's sense of justice if an inventor could receive a patent upon a composition of matter, setting out at length in the specification the useful purposes of such composition, manufacture and sell it to the public, and then prevent the public from making any beneficial use of such product by securing patents upon each of the uses to which it may be adapted.

Pet. App. 13a. But that sentence—written 20 years before the enactment of section 100(b) in 1952—does not even purport to apply where new uses are the result of subsequent innovation. As the Federal Circuit dissenters observed, allowing the new-use patent in this circumstance cannot shock the sense of justice. Pet. App. 139a. It is, indeed, what section 100(b) contemplates.

Not surprisingly, no matter how read, the sentence from *Byck* does not represent the holding or even the rationale of that case. In *Byck*, the inventor had previously patented a certain "phenolic condensation product." *Byck*, 48 F.2d at 666. Byck then sought to obtain claims to a coil coated with the same product. *Id.* at 665. The court held that these claims were unpatentable for double patenting, *not* because that use was disclosed in Byck's earlier patent, but because that use would have been

"obvious" "in view of the [prior art] Baekeland reference." *Id.* at 666-67. *Byck* is thus an example of a traditional claim-to-claim obviousness analysis in view of prior art.

Nor does *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, 518 F.3d 1353 (Fed. Cir. 2008), which the panel here also cited, support this new rule. In *Pfizer*, a later patent claimed the method of using, to combat inflammation, non-steroidal compositions that an earlier patent claimed. *Id.* at 1363 & n.9. But there, as the parties stipulated, the *claims* of the earlier patent themselves *recited* the utility of inducing an "anti-inflammatory" response. 482 F. Supp. 2d 390, 477 (D.N.J. 2007).[10] Accordingly, the district court held that "reliance on the specification is *not even necessary* for one to glean the common utility in this case." *Id.* (emphasis added). In affirming the district court, the Federal Circuit specifically relied on the stipulation to invalidate the second patent's claims to anti-inflammatory uses (518 F.3d at 1363), and held the other claimed uses obvious from the anti-inflammatory use (*id.* at n.9).

In short, neither *Geneva* nor *Byck* nor *Pfizer* is precedent for the present panel's new bright-line rule. That rule is a radical departure from long-established precedent.

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[10] The trial court stated: "The parties have stipulated that the term 'therapeutically effective amount' in the asserted claims of [both] the *** Patents means the same thing—an amount of active ingredient that would elicit an anti-inflammatory or analgesic response ***." *Id.*

II. The Panel's New Rule Conflicts with the Patent Statute

The panel's rule is not just contrary to precedent. It is contrary to all that the patent *statute* has to say on the subject. It is impermissible to apply a judge-made rule in a manner that actually conflicts with a statute. *See United States v. Oakland Cannabis Buyers' Coop.*, 532 U.S. 483, 497 (2001) (in exercising equitable powers, a district court "cannot *** override Congress' policy choice, articulated in a statute, as to what behavior should be prohibited"); *United States v. Noland*, 517 U.S. 535, 543 (1996) (equitable subordination doctrine cannot contradict congressional choice); *Nw. Airlines, Inc. v. Transp. Workers Union of Am.*, 451 U.S. 77, 95 (1981) ("[F]ederal common law is 'subject to the paramount authority of Congress.'"); *Moragne v. States Marine Lines, Inc.*, 398 U.S. 375, 390-93 (1970) (federal common law must accord with statutory choices).

The foundation for any double-patenting doctrine is the section 101 requirement that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain *a patent* therefor, subject to the conditions and requirements of this title." (Emphasis added). The singular "a patent" is the direct source for the "same invention" bar on double patenting and the indirect source for the "obviousness-type" double-patenting bar.

The plain focus of section 101 is on what the patent is granted "[]for"—which means the invention that is *claimed*. Moreover, the "[w]hoever" that may obtain a patent on its face includes anyone, including those who have made earlier, related inventions. Further, this provision itself separates "process" inventions from "composition[s] of matter" (and machines and manufactures), and section 100(b) expressly defines "process" to include "a new use of a known *** composition of matter." The inventor of a new use of a known composition of matter, even if he is also the inventor of the composition of matter, is plainly entitled to a patent for the new use—subject to the other "conditions and requirements of this title."

No provision of the Patent Act disqualifies that inventor based on *disclosures* (by himself or by others) of his invention like the single paragraph added to the '614 specification here on the day the application for the '826 patent was filed. *See, e.g., In re Katz*, 687 F.2d 450, 454 (CCPA 1982) (patentability foreclosed only by section 102(b) for publication more than one year before filing). Upon filing of the application for the '826 patent, the inventors here were entitled to shout their invention from the rooftops without loss of the right to patent it. Accordingly, the disclosure of the invention on that day in a related patent application cannot justify a contrary result.

Obviousness-type double patenting must, therefore, rely on the policy deemed implicit in the one-patent command of section 101: mere obvious

variations of an invention staked out in an earlier patent cannot be again staked out in a later patent. But that principle concerns the *claimed* invention, not a mere non-prior-art disclosure, and it most pointedly cannot preclude patenting a nonobvious new use of a known composition.

In breaching the commands of sections 100(b) and 101, the Federal Circuit also ran afoul of yet another statutory provision, section 120, which can be critical to the essential question of when a first invention has been completed. The panel refused to evaluate the invention claimed in the '614 patent as of its 1983 effective filing date, instead relying on matter added to the patent's text afterwards, *i.e.*, the anticancer use that was nowhere mentioned in the original 1983 application. Section 120, following the decision from which it was derived, *Godfrey v. Eames*, 68 U.S. 317 (1863), precludes that result. Later-added matter may not be given an effect that alters the "legal consequences" flowing from a sufficient original disclosure. *Id.* at 324-25.

Finally, the impropriety of the Federal Circuit's rule is starkly illustrated by the facts of this case, where its application puts that judge-made doctrine at odds with the express statutory obviousness provision. As is undisputed, the earlier patent claims here are actually prior art to the later patent claims—so that section 103 itself directly applies for the assessment of obviousness of the later over the earlier. Another federal district court has in fact adjudicated that issue and found *non*obviousness. *See* pp. 14-15, *supra*. But the

Federal Circuit's ruling made such an adjudication legally immaterial. The panel concluded that even if the '826 patent claims are nonobvious from the '614 patent claims, they are nevertheless invalid for obviousness-type double patenting.

The judge-made law of double patenting was created to fill a void in the Patent Act where an earlier patent claim is not prior art to a later patent claim, *i.e.*, where patentable distinctness of the later claim is not assured by operation of section 103. *See* Robert P. Merges and John Fitzgerald Duffy, *Patent Law and Policy: Cases and Materials* 1207 (4th ed. 2007). Thus, application of the double patenting doctrine where section 103 *does* provide the test for patentable distinctness is unnecessary and illogical.[11]

Even if the double patenting and obviousness analyses were both applicable, obviousness-type double patenting cannot properly be found where section 103 applies and nonobviousness is found. In *In re Land*, 368 F.2d 866, 884 (CCPA 1966), the court so concluded, explaining: "As to the claims on

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[11] As the Federal Circuit dissenters here stated, "[a] double patenting analysis occurs *only* when the earlier patent is not prior art against the later patent." Pet. App. 135a (emphasis added); *see In re Ornitz*, 376 F.2d 330, 334 (CCPA 1967) ("While 'double patenting' rejections are made ***, this is done because the reference relied on is not 'prior art' ***. Where it is possible to conduct the *broader* inquiry permitted by sections 102(e) and 103 because the references are 'prior art,' it does not make sense to resort to the *narrower* inquiry which underlies a 'double patenting' rejection ") (emphasis added).

which we have reversed the obviousness rejection, a fortiori this double patenting rejection, predicated on obviousness, would be reversed for the same reasons."[12] The panel decision in this case conflicts with that sound principle.

In short, judge-made "obviousness-type double patenting" cannot exist where the statutory obviousness inquiry under section 103 in view of a prior art patent is applicable and results in a finding of nonobviousness for the later-patented claim. Under such circumstances, the later-patented claim cannot represent an unjustified timewise extension of patent rights with respect to the earlier-patented claims. Once the existence of a separate and patentably distinct invention is confirmed by section 103, (1) the legal standard for avoiding "obviousness-type double patenting" has been met; (2) any policy justification for finding "obviousness-type double patenting" has been extinguished; and (3) the second inventor is entitled to a separate patent on the nonobvious improvement over the prior art.

As reflected in its opinion (Pet. App. 12a n.3), the panel drifted into the above-described conflict with precedent and the statute out of an overriding

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[12] *See also Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 999 (Fed. Cir. 2009) (nonobviousness under § 103 forecloses obviousness-type double patenting); *In re White*, 405 F.2d 904, 906 (CCPA 1969) (same); *In re Jezl*, 396 F 2d 1009, 1013 (CCPA 1968) (same); *Eli Lilly and Co. v. Zenith Goldline Pharms., Inc.*, 364 F Supp. 2d 820, 910 (S.D. Ind. 2005), *aff'd*, 471 F.3d 1369 (Fed Cir. 2006) (same).

concern with cases where an original application discloses multiple utilities, and it is unclear whether one of them was a separate and subsequent invention. But in *this* case there cannot possibly be any doubt: the anticancer utility was invented and added *after* the original application. In any event, a blanket rule is not justified by the possibility that, where an original application discloses multiple utilities, a determination of which inventions were separate from and subsequent to others requires examining evidence beyond the face of the document. This Court has clearly stated that such bright-line rules are not justified simply because they are easy to apply. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 32 n.6 (1997).

III. The Panel's New Rule Subverts the Disclosure Policies Underlying the Patent Statute

The Federal Circuit's new rule of law discourages rather than promotes public disclosure of new inventions. The panel's new rule penalizes supplemental disclosure of a subsequently discovered new use: an applicant for a basic patent, having discovered a new and nonobvious use after filing his application for the basic invention, cannot add that disclosure to his application without losing the normal right to secure a separate patent on the new use. Lilly's disclosure of the later-discovered, preferred use for gemcitabine in the '614 patent served only to aid the public by promoting early disclosure of a beneficial new use of a compound resulting from a subsequent invention.

Thomas Jefferson, who was "the driving force behind early federal patent policy" (*Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 147 (1989)), wrote that a patent is a "reward, *an inducement, to bring forth new knowledge*." *Graham*, 383 U.S. at 8-9 n.2 (citing VI *The Writings of Thomas Jefferson*, at 180-81 (H.A. Washington ed. 1859)) (emphasis added). "[T]he ultimate goal of the patent system is to bring new designs and technologies into the public domain through *disclosure*." *Bonito Boats*, 489 U.S. at 977-78 (emphasis added). "As a reward for inventions and to *encourage their disclosure*, the United States offers a [limited] monopoly to an inventor who refrains from keeping his invention a trade secret." *Universal Oil Prods. Co. v. Globe Oil & Refining Co.*, 322 U.S. 471, 484 (1944) (emphasis added).

Indeed, the impropriety of the panel's bright-line rule here is highlighted by the fact that the new use could have been validly patented here if only it had been *concealed* from readers of the first patent. Mandatory concealment once an application for the invention is filed has no place in a rational patent system intended to promote disclosure. Punishing a patentee, such as Lilly, for its early disclosure of a later-discovered, distinct invention "subvert[s] the patent system's goal of promoting the useful arts through encouraging early disclosure." *Transco*, 38 F.3d at 558.

IV. This Court's Review Is Necessary and Appropriate

This Court has not spoken on the largely judge-made double-patenting doctrine since the 1952 Act became law. The Federal Circuit has now transformed the doctrine to contradict the statute and this Court's and its own (and predecessor court's) precedents. Authoritative guidance is sorely needed.

Over the objections of four of its members, the Federal Circuit has decided not to rehear this case en banc. Those four judges recognize that the panel opinion conflicts with binding precedent. Under the Federal Circuit's own precedent (*see* n.7, *supra*), judges who see such an inter-panel conflict should follow the earlier decisions if the same or a similar issue arises in the next case, leaving the outcome uncertain and dependent on the assignment of panel members. Thus, the denial of rehearing en banc "leaves the innovation community," the PTO in processing patent applications, district courts, patent owners, and patent challengers, "without guidance" on which to rely. Pet. App. 141a. This kind of disruptive uncertainty in the law is exactly what the Federal Circuit was created to avoid.

Reversal of the panel's new bright-line rule is also needed to avoid disrupting the settled expectations of the inventing community. This Court has more than once cautioned that "courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)

(quoting *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 199 (1933)); *Diamond v. Diehr*, 450 U.S. 175, 182 (1981). This Court cautioned the Federal Circuit in both *Warner-Jenkinson,* 520 U.S. at 28, 32 n.6, and *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002), to avoid the creation of new rules that upset the settled expectations of the patent community. Specifically, in *Festo*, this Court stated that the Federal Circuit "ignored the guidance of *Warner-Jenkinson*, which instructed that courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community. *** The responsibility for changing them rests with Congress. *** Fundamental alterations in these rules risk destroying the legitimate expectations of inventors in their property." *Festo*, 535 U.S. at 739.

The problem is particularly acute where, as here, a rigid new rule has been adopted that alters a flexible standard of long standing. *See, e.g.*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007) (reversing rigid application of flexible obviousness standards); *eBay Inc. v. Mercexchange, L.L.C.*, 547 U.S. 388, 392-94 (2006) (rejecting the Federal Circuit's bright-line grant of permanent injunctions when validity and infringement have been found); *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 60, 63 (1998) (rejecting a bright-line rule that an invention cannot be "on sale" unless and until it is reduced to practice); *Bilski v. Kappos*, 130 S. Ct. 3218, 3226-27 (2010) (rejecting machine-or-transformation test as exclusive way to assess patentable subject matter under § 101). Here, in conflict with such precedent,

the panel's rigid bright-line rule destroys the settled expectations and property rights of patent holders.

This decision is especially harmful to important industries like the biotechnology and pharmaceutical industries, as reflected by the amicus support for en banc review by major industry organizations PhRMA and the Biotechnology Industry Organization. These industries are heavily dependent on very large, long-term investments based on stable and predictable patent laws. The announcement and retroactive application of new, law-changing rules, years or decades after investment decisions have been made, do significant damage to such industries, creating a profound disincentive to invest the hundreds of millions of dollars necessary to bring a new pharmaceutical product to market. That is a grave consequence at a time when, as the Government recognizes, the public needs such investment in drug development to increase. *See* Gardiner Harris, *Federal Research Center Will Help Develop Medicines*, N.Y. Times, Jan. 23, 2011, at A1 ("The Obama administration has become so concerned about the slowing pace of new drugs coming out of the pharmaceutical industry that officials have decided to start a billion-dollar government center to help create medicines.").

CONCLUSION

For all the above reasons, Lilly respectfully requests that the Court grant its petition for a writ of certiorari.

Respectfully submitted,

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APPENDIX

Appendix A

United States Court of Appeals
for the Federal Circuit

SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Plaintiff-Appellee,

v.

ELI LILLY AND COMPANY,
Defendant-Appellant.

2010-1105

Appeal from the United States District Court for the Eastern District of Michigan in case no. 07-CV-15087, Judge George Caram Steeh.

Decided: July 28, 2010

JAMES F. HURST, Winston & Strawn LLP, of Chicago, Illinois, argued for plaintiff-appellee. With him on the brief were GAIL J. STANDISH and PETER E. PERKOWSKI, of Los Angeles, California.

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Reston, Virginia, argued for defendant-appellant. With him on the brief were ROBERT D. BAJEFSKY, HOWARD W. LEVINE, ROBERT F. SHAFFER and JESSICA R.

UNDERWOOD, of Washington, DC. Of counsel on the brief was JAMES P. LEEDS, Eli Lilly and Company, of Indianapolis, Indiana.

Before BRYSON, GAJARSA, and PROST, *Circuit Judges*. PROST, *Circuit Judge*.

Appellant Eli Lilly and Company ("Lilly") appeals from a final judgment of the U.S. District Court for the Eastern District of Michigan, finding claims 2, 6, and 7 of U.S. Patent No. 5,464,826 ("'826 patent") invalid for obviousness-type double patenting over U.S. Patent No. 4,808,614 ("'614 patent"). Because the district court correctly found these claims of the '826 patent invalid, we affirm.

BACKGROUND

Lilly markets the drug Gemzar® for the treatment of various forms of cancer. The active ingredient in Gemzar® is gemcitabine. Both patents at issue in this suit, the '614 patent and the '826 patent, cover gemcitabine and are therefore listed in the Food and Drug Administration's ("FDA's") Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") with respect to Gemzar®. The '614 patent claims gemcitabine, as well as a method of using gemcitabine for treating viral infections. The '826 patent, however, claims a method of using gemcitabine for treating cancer.

The '614 patent, entitled "Difluoro Antivirals and Intermediate Therefor," issued on February 28, 1989 and expired on May 15, 2010. The '614 patent resulted from a divisional application, filed December 4, 1984, as a continuation-in-part of U.S. Patent Application Serial No. 473,883 ("original '883 application"), filed on March 10, 1983.[1] '614 patent at [60], col.1 ll.7-11.

The specification of the original '883 application described only gemcitabine's utility for antiviral purposes. The continuation-in-part that resulted in the '614 patent added a description of gemcitabine's anticancer utility to the specification. Specifically, the specification of the '614 patent explains:

> In addition to the antiviral utility of the present compounds, certain of the compounds of the present invention have also demonstrated *excellent oncolytic activity* in standard cancer screens. A *particularly preferred compound with this utility is [gemcitabine].* This compound demonstrated activity in tumor systems L1210V lymphocytic leukemia,

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[1] Lilly and Sun Pharmaceutical Industries, Ltd. ("Sun") did not dispute before the district court or on appeal that the '614 patent is entitled to the benefit of the filing date of the original '883 application. *See* Lilly's Principal Br. 8, 21; Lilly's Reply Br. 12, 19.

> 6C3HED lymphosarcoma, CA-755 adenocarcinoma, P1534J lymphatic leukemia and X5563 plasma cell myeloma.

Id. col.17 ll.53-63 (emphases added). Claims 1, 2, and 8 of the '614 patent are directed to a class of nucleosides, which includes gemcitabine, whereas dependent claim 12 is directed solely to gemcitabine. *Id.* col. 19. l.56-col.22 l.15. Claims 13 and 14 of the '614 patent recite a method of using the claimed nucleosides, including gemcitabine, for treating Herpes viral infections. *Id.* col.22 ll.16-24. The '614 patent does not claim a method of using any of the claimed nucleosides for treating cancer.

On December 4, 1984, the same day that Lilly filed the continuation-in-part that resulted in the '614 patent, Lilly filed another patent application that ultimately issued as the '826 patent. The '826 patent, titled "Method of Treating Tumors in Mammals with 2',2'Difluoronucleosides," issued on November 7, 1995. The '826 patent expires on November 7, 2012, which is two-and-a-half years after the expiration of the '614 patent. Lilly did not file a terminal disclaimer with respect to the '826 patent.

Each claim of the '826 patent is directed to a method of treating cancer with an effective amount of a class of nucleosides, which includes gemcitabine. Specifically, claim 1 of the '826 patent recites "[a] method of treating susceptible neoplasms[, i.e., cancer,] in mammals comprising administering to a

mammal in need of such treatment a therapeutically effective amount" of the class of nucleosides. '826 patent col.23 l.41-col.24 l.46. Claim 2 of the '826 patent, which depends from claim 1, is specifically directed to a method of using gemcitabine "or a pharmaceutically acceptable salt thereof" for this purpose. *Id.* col.24 ll.46-48. Dependent claims 6 and 7 are directed to treating specific "susceptible neoplasms," including "leukemias, sarcomas, carcinomas, and myelomas," with the entire class of nucleosides and gemcitabine respectively. *Id.* col.24 ll.59-64.

In 2006, Sun, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") with the FDA in which Sun sought approval to market a generic version of Lilly's Gemzar® and certified that both the '614 patent and the '826 patent were invalid or not infringed. On November 29, 2007, Sun filed this declaratory judgment action against Lilly, seeking declaratory relief that the '826 patent is invalid and not infringed. Lilly filed counterclaims for infringement of the '826 patent and the '614 patent.

On August 17, 2009, the district court granted Sun's motion for partial summary judgment that the asserted claims, namely claims 2, 6, and 7, of the later '826 patent are invalid for obviousness-type double patenting over the earlier '614 patent. *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 647 F. Supp. 2d 820 (E.D. Mich. 2009) ("*Summary Judgment Order*"). Relying primarily on our decisions in *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline*

PLC, 349 F.3d 1373 (Fed. Cir. 2003), and *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, 518 F.3d 1353 (Fed. Cir. 2008), the district court concluded that, given the '614 patent's disclosure of gemcitabine's anticancer use, claim 12 of the earlier '614 patent, which claims gemcitabine, and claims 2, 6, and 7 of the later '826 patent, which claim a method of using gemcitabine for cancer treatment, are not patentably distinct as a matter of law. *Summary Judgment Order*, 647 F. Supp. 2d at 824-25.

Upon motion by Lilly, the district court, pursuant to Federal Rule of Civil Procedure 54(b), entered final judgment that the '826 patent is invalid. Lilly timely appealed to this court. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

"Double patenting is a question of law, which we review without deference." *Pfizer*, 518 F.3d at 1363. Similarly, we review "a district court's grant of summary judgment without deference." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1372 (Fed. Cir. 2005). "A court considering summary judgment must draw all reasonable inferences in favor of the nonmovant." *Geneva*, 349 F.3d at 1379.

"The doctrine of double patenting is intended to prevent a patentee from obtaining a timewise extension of [a] patent for the same invention or an obvious modification thereof." *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1375 (Fed. Cir. 2008). The proscription against double

patenting takes two forms: (1) statutory double patenting, which stems from 35 U.S.C. § 101 and prohibits a later patent from covering the same invention, i.e., identical subject matter, as an earlier patent, and (2) obviousness-type double patenting, which is a judicially created doctrine that prevents a later patent from covering a slight variation of an earlier patented invention. *Perricone*, 432 F.3d at 1372-73; *see Geneva*, 349 F.3d at 1377-78.

The second type of double patenting, obviousness-type double patenting, prohibits "claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." *In re Basell*, 547 F.3d at 1375. An obviousness-type double patenting analysis, which "compares claims in an earlier patent to claims in a later patent or application," *Geneva*, 349 F.3d at 1378 n.1, consists of two steps, *Pfizer*, 518 F.3d at 1363. First, the court "construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences." *Id.* Second, the court "determines whether those differences render the claims patentably distinct." *Id.* "A later claim that is not patentably distinct from," i.e., "is obvious over[] or anticipated by," an earlier claim is invalid for obviousness-type double patenting. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001).

Our prior obviousness-type double patenting decisions in *Geneva* and Pfizer, which addressed factual situations closely resembling that presently before the court, control this case. In both cases, we found claims of a later patent invalid for

obviousness-type double patenting where an earlier patent claimed a compound, disclosing its utility in the specification, and a later patent claimed a method of using the compound for a use described in the specification of the earlier patent. *See Pfizer*, 518 F.3d at 1363; *Geneva*, 349 F.3d at 1385-86. We held that a "claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use." *Pfizer*, 518 F.3d at 1363; *Geneva*, 349 F.3d at 1385-86.

In *Geneva*, the earlier patent claimed a compound, potassium clavulanate, and the specification disclosed its effectiveness in inhibiting ß-lactamase in humans. 349 F.3d at 1384-86. The later patent then claimed a method of using the compound to effect ß-lactamase inhibition in humans or animals. *Id.* In our obviousness-type double patenting analysis, we determined that to ascertain the scope of the earlier patent's claim to the compound itself, we had to examine the specification of the earlier patent, including the compound's disclosed utility. *Id.* at 1385. Upon reviewing this disclosure, we concluded that the claims of the two patents were not "patentably distinct" and thus the later patent was invalid for obviousness-type double patenting, because the later patent "claim[ed] nothing more than [the earlier patent's] disclosed utility as a method of using the . . . compound." *Id.* at 1385-86.

Similarly, in *Pfizer*, the earlier patent claimed several compounds and the specification disclosed

their use in treating inflammation and inflammation-associated disorders. 518 F.3d at 1363 & n.9; *see* U.S. Patent No. 5,563,165 ("'165 patent"), at [57], col.1 ll.11-14, col.3 ll.3-27. The later patent then claimed a method of using these compounds for treating inflammation, inflammation-associated disorders, and specific inflammation-associated disorders, including arthritis, pain, and fever. *Pfizer*, 518 F.3d at 1363 & n.9; *see* U.S. Patent No. 5,760,068 ("'068 patent") col.97 l.49-col.108 l.29. After rejecting the patentee's objection to our consideration of the specification of the earlier patent, we determined that the later patent "merely claims a particular use described in the [earlier] patent of the claimed compositions of the [earlier] patent." *Pfizer*, 518 F.3d at 1363 & n.8. As such, we concluded that the asserted claims of the later patent were not "patentably distinct" from the claims of the earlier patent, and thus the later patent was invalid for obviousness-type double patenting. *Id.* at 1368.

Lilly attempts to distinguish *Geneva* and *Pfizer* from this case, arguing that the holding of these cases should be limited to their facts. Lilly contends that in both cases, the specification of the earlier patent disclosed a single use for the claimed compound, which was an essential part of the patented invention and thus necessary to patentability. Lilly argues that the double-patenting analysis of *Geneva* and *Pfizer* does not apply to the later '826 patent claims reciting a method of using gemcitabine for cancer treatment because, though the specification of the earlier '614 patent disclosed

gemcitabine's use in treating both viral infections and cancer, the antiviral use provided the essential utility necessary to the patentability of the '614 patent's claim to gemcitabine. Lilly objects to what it characterizes as the district court's extension of the obviousness-type double patenting analysis of *Geneva* and *Pfizer* to any utility disclosed in the specification of an earlier patent. We reject Lilly's argument.

It is true that, as the *Geneva* court recognized, the earlier patent in *Geneva* disclosed a "single use" for the claimed compound, namely inhibition of ß-lactamase. 349 F.3d at 1384-86. However, the reasoning and holding of *Geneva* are not so limited. *Id.* Our later decision in *Pfizer* demonstrates this point. We disagree with Lilly's attempt to characterize *Pfizer* as involving a single disclosed utility, as well as with its argument that the decision's rationale turned on this alleged single utility.

First, Lilly's classification of *Pfizer* is factually erroneous because the earlier patent's specification unambiguously disclosed more than one utility for the claimed compound. Specifically, the specification of the earlier patent described the compound's use in treating both inflammation *and* inflammation-associated disorders.[2] The specification also

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[2] *See, e.g.*, '165 patent, at [57] ("A class of . . . compounds is described for use in treating inflammation *and* inflammation-related disorders.") (emphasis added), *id.* col 1 ll 11-14 ("This invention . . . specifically relates to

(continued...)

enumerated nearly fifty different inflammation-associated disorders, including pain, headaches, fever, arthritis, asthma, bronchitis, skin-related conditions, and gastrointestinal conditions, for which the claimed compounds "would be useful." '165 patent col.3 ll.3-27. The specification's discussion of the compounds' use for both inflammation and inflammation-associated disorders, as well as the diverse range of ailments expressly included in the "inflammation-associated disorders" category, shows that the specification disclosed more than one use for the claimed compounds. The later patent even claimed the compounds' use for inflammation, inflammation-associated disorders, and specific inflammation-associated disorders, including arthritis, pain, and fever, in separate dependent claims, further evidencing that the utilities disclosed in the specification of the earlier patent are distinct. *See* '068 patent col. 108 ll.18-27. Therefore, we do not agree that *Pfizer* involved a single disclosed utility that was alone essential to the patentability of the claimed compounds.

Moreover, the analysis in the *Pfizer* decision shows that obviousness-type double patenting encompasses any use for a compound that is disclosed in the specification of an earlier patent

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(...continued)

compounds . . for treating inflammation *and* inflammation-associated disorders, such as arthritis ") (emphasis added), *id.* col.3 ll.3-27 ("Compounds of Formula I would be useful for the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders ") (emphasis added)

claiming the compound and is later claimed as a method of using that compound. *Pfizer* never implies that its reasoning depends in any way on the number of uses disclosed in the specification of the earlier patent. *See* 518 F.3d at 1363. Instead, its broad analysis reflects that the court considered the multiple uses for the compound that were discussed in the specification of the earlier patent. Indeed, the *Pfizer* decision ultimately invalidated claims in the later patent that were separately directed to these multiple uses, including inflammation, inflammation-associated disorders, and the specific inflammation-associated disorders of arthritis, pain, and fever. *Id.* at 1363 & n.9; *see* '068 patent col.108 ll.18-27.

Thus, the holding of *Geneva* and *Pfizer*, that a "claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use," extends to any and all such uses disclosed in the specification of the earlier patent.[3]

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[3] In rejecting Lilly's proposed single, essential utility test, we also note that such a test would be unworkable. Where an earlier patent specification describes multiple uses for a compound, a court would be unable to identify the one use that was "essential" or "necessary" to patentability. Indeed, Lilly's counsel repeatedly conceded at oral argument that "many times [a court] may not able to tell" which use was essential to patentability, as would be required under Lilly's test. Oral Arg. at 3:39-6:03, *available at* http://oralarguments.cafc.uscourts.gov/mp3/2010-1105.mp3; *see id.* at 9:48-10 42 ("In many cases, we concede th[is] could be a difficult inquiry."), *id* at 13:20-13:58. Additionally, the (continued...)

Pfizer, 518 F.3d at 1363; *Geneva*, 349 F.3d at 1385-86. Indeed, as both cases recognized,

> [i]t would shock one's sense of justice if an inventor could receive a patent upon a composition of matter, *setting out at length in the specification* the *useful purposes* of such composition, . . . and then prevent the public from making any beneficial use of such product by securing patents *upon each of the uses* to which it may be adapted.

Pfizer, 518 F.3d at 1363 n.8 (emphases added); *Geneva*, 349 F.3d at 1386 (quoting *In re Byck*, 48 F.2d 665, 666 (CCPA 1931)).

Furthermore, we reject Lilly's argument that the district court erred in consulting the specification of the issued '614 patent, as opposed to the specification of an earlier application, to ascertain the relevant disclosed uses of the compound gemcitabine for its obviousness-type double patenting analysis. Both *Geneva* and *Pfizer* make clear that, where a patent features a claim directed to a compound, a court must consider the specification because the disclosed uses of the

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(...continued)

characterization of the single essential utility might be arbitrary in application. For example, a broadly defined "single" utility might in actuality encompass multiple utilities, leading to significant problems in applying Lilly's proposed standard.

compound affect the scope of the claim for obviousness-type double patenting purposes. In *Geneva*, we acknowledged the general rule that an earlier patent's specification is not available to show obviousness-type double patenting. 349 F.3d at 1385. We have held, however, that there are "certain instances" where the specification of an earlier patent may be used in the obviousness-type double patenting analysis. *In re Basell*, 547 F.3d at 1378. Specifically, the specification's disclosure may be used to determine whether a claim "merely define[s] an obvious variation of what is earlier disclosed and claimed," "to learn the meaning of [claim] terms," and to "interpret[] the coverage of [a] claim." *Id.* As we recognized in *Geneva*, a court considering a claim to a compound must examine the patent's specification to ascertain the coverage of the claim, because a claim to a compound "[s]tanding alone . . . does not adequately disclose the patentable bounds of the invention." 349 F.3d at 1385. In examining the specification of the earlier patent, the court must consider "the compound's disclosed utility." *Id.*

We affirmed this holding in *Pfizer* by rejecting the patentee's objection to our reliance on the specification of the earlier patent that claimed the compounds at issue and explaining that "[t]here is nothing that prevents us from looking to the specification to determine the proper scope of the claims." *Pfizer*, 518 F.3d at 1363 (citing *Geneva*, 349 F.3d at 1386). Thus, we have expressly held that, where a patent claims a compound, a court performing an obviousness-type double patenting

analysis should examine the specification to ascertain the coverage of the claim.

In response to Lilly's arguments, we determine that where such examination of the specification is appropriate in an obviousness-type double patenting analysis, the specification that must be considered is that of the issued patent. Lilly contends that the district court should have evaluated the '614 patent's claim to gemcitabine based on the specification that existed as of the undisputed effective filing date of the '614 patent, namely the specification of the original '883 application. The original '883 application disclosed only gemcitabine's antiviral use, not its anticancer use; Lilly added a description of gemcitabine's anticancer use to the specification in a continuation-in-part application that eventually resulted in the '614 patent. Lilly therefore asks this court to ignore the '614 patent's description of gemcitabine's use in cancer treatment, because this disclosure was not part of the original '883 application.

To support this argument, Lilly cites only the basic tenet of claim construction, as stated in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005), that claim terms should be given their ordinary and customary meaning and this meaning is the one that "the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, however, does not support the proposition that a court should ignore portions of the patent specification in construing

claims. Instead, *Phillips* makes clear that claim terms must be construed in light of the entirety of the patent, including its specification, and that the specification to be consulted is that of the issued patent, not an earlier application.

Specifically, *Phillips*, as well as the rest of our claim construction precedent, expounds that a "person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the *entire patent, including the specification*." *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1374 (Fed. Cir. 2009) (emphasis added); *Aquatex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1380 (Fed. Cir. 2005); *Phillips*, 415 F.3d at 1313. In other words, "the 'ordinary meaning' of a claim term is its meaning to the ordinary artisan after reading the *entire patent*." *ICU Med.*, 558 F.3d at 1375 (emphasis added); *Phillips*, 415 F.3d at 1321. *Phillips* further explains the "fundamental rule" that claim terms "are construed with *the meaning with which they are presented in the patent document*." 415 F.3d at 1316 (emphasis added). As such, "[t]he construction that stays true to the claim language and most naturally aligns with *the patent's description* of the invention will be . . . the correct construction." *Id.* (emphasis added).

In sum, our claim construction precedent establishes that claim terms must be construed in light of the entire issued patent. This precedent leaves no room for debate that the relevant

specification for claim construction purposes is that of the issued patent, not an early version of the specification that may have been substantially altered throughout prosecution. There is no support for Lilly's argument that the district court should have consulted the specification of the original '883 application, which was changed before the '614 patent issued, to construe the issued patent claims. Lilly cannot avoid portions of the specification of the '614 patent by resorting to the specification as originally filed.

We note that, where necessary in the obviousness-type double patenting analysis, consulting the specification of the issued patent, as opposed to an earlier version of the specification, is consistent with the policy behind double patenting. As we stated in *In re Kaplan*, 789 F.2d 1574, 1579-80 (Fed. Cir. 1986), "[a]ll proper double patenting rejections, of either type, rest on the fact that a patent has been *issued* and later issuance of a second patent will continue protection, beyond the date of expiration of the first patent" of the same invention or an obvious variation thereof. In other words, the double patenting doctrine is concerned with the issued patent and the invention disclosed in that issued patent, not earlier drafts of the patent disclosure and claims.

In conclusion, the district court correctly followed the double patenting analysis of the *Geneva* line of cases, which address the situation in which an earlier patent claims a compound, disclosing the utility of that compound in the specification, and a

later patent claims a method of using that compound for a particular use described in the specification of the earlier patent. As the district court recognized, claim 12 of the earlier '614 patent claims the compound gemcitabine. Following our precedent in *Geneva*, the district court properly considered the uses for gemcitabine disclosed in the specification of the issued '614 patent, specifically its use in treating viral infections and cancer, to determine the scope of this claim. *See Geneva*, 349 F.3d at 1385; *Summary Judgment Order*, 647 F. Supp. 2d at 824-25. In light of the earlier '614 patent's description of gemcitabine's use in treating cancer, the asserted claims of the later '826 patent, which recite a method of using gemcitabine to treat cancer, are not patentably distinct from the '614 patent's claim to gemcitabine. The asserted claims of the later '826 patent simply claim the anticancer use disclosed in the specification of the '614 patent as a method of use claim. *See Pfizer*, 518 F.3d at 1363; *Geneva*, 349 F.3d at 1385. Therefore, we affirm the district court's judgment that the asserted claims, claims 2, 6, and 7, of the '826 patent are invalid for obviousness-type double patenting over the '614 patent.

AFFIRMED

Appendix B

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

SUN
PHARMACEUTICAL
INDUSTRIES, LTD.,

Plaintiff,

vs.

Case No. 07-CV-15087
HON. GEORGE CARAM
STEEH

ELI LILLY AND
COMPANY,

Defendant.
_____/

ORDER GRANTING PLAINTIFF SUN PHARMACEUTICALS' MOTION FOR PARTIAL SUMMARY JUDGMENT (# 45)

Plaintiff Sun Pharmaceuticals moves for partial summary judgment of invalidity of the asserted claims of defendant Eli Lilly and Company's U.S. Patent 5,464,826 ("'826 Patent"). A hearing was held on July 24, 2009. For the reasons set forth below, Sun Pharmaceuticals' motion for partial summary judgment will be GRANTED.

I. Background

Sun Pharmaceuticals filed a complaint on November 29, 2007 alleging it has submitted an

Abbreviated New Drug Application ("ANDA") with the FDA to market its generic version of Eli Lilly's cancer medication "Gemzar" (gemcitabine). Eli Lilly holds the '826 Patent, a patent listed in the FDA's "Orange Book." Sun Pharmaceuticals wants to market its generic version of the patented drug before Eli Lilly's '826 Patent expires. The Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j), required Sun Pharmaceuticals to: (1) certify to the FDA that its generic drug will not infringe the '826 Patent; and (2) notify Eli Lilly of this certification. Sun Pharmaceuticals seeks declaratory relief that the '826 Patent is invalid, and alternatively, that its generic drug does not infringe the '826 Patent. Eli Lilly filed counterclaims of infringement of its '826 Patent and U.S. Patent 4,808,614 ("'614 Patent") on January 7, 2008.

II. Motion for Partial Summary Judgment

Sun Pharmaceuticals moves for partial summary judgment of its claim that Eli Lilly's '826 Patent is invalid pursuant to the judicially created doctrine of "obviousness-type double patenting," a doctrine that "prohibit[s] a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc., 518 F.3d 1353, 1363 (Fed. Cir. 2008) (quoting Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 967 (Fed Cir. 2001)). The patents at issue here are the commonly owned earlier '614 Patent and the later '826 Patent.

A. '614 Patent

The '614 Patent issued on February 28,1989 and is titled "DIFLUORO ANTIVIRALS AND INTERMEDIATE THEREFORE." The "ABSTRACT" reads "A 2,2-difluoro-2-deoxycarbohydrate is used to prepare antiviral nucleosides." The "SUMMARY OF THE INVENTION" provides in part:

> Pharmaceutical compositions comprising a nucleoside of the above formula and a pharmaceutically acceptable carrier, diluent or excipient therefor are provided as yet another aspect of the present invention, as is a method of treating viral infections in mammals employing a present novel compound.

(emphasis added). Within the "DESCRIPTION OF THE PREFERRED EMBODIMENTS," the '614 Patent describes the "specific nucleosides ... to assure that every reader understands the type of antivirals which this invention makes available." (emphasis added). After giving eleven examples of compounds, the '614 Patent continues:

> In addition to the antiviral utility of the present compounds, certain of the compounds of the present invention have also demonstrated excellent oncolytic activity in standard cancer

> screens. A particularly preferred compound with this utility is the compound of Example 8 [gemcitabine] . . .
>
> This compound demonstrated activity in tumor systems L1210V lymphocytic leukemia, 6C3HED lymphosarcoma, CA-755 adenocarcinoma, P1534J lymphatic leukemia and X5563 plasma cell myeloma. When used for cancer chemotherapy, dosages per day of the active compounds will be in the range of about 0.1 to about 1200 mg./kg. of body weight. In the treatment of adult humans, the range of about 0.1 to about 50 mg./kg., in single or divided doses, is preferred.

(emphasis added). The pertinent claims of the '614 Patent read:

> 1. A nucleoside of the formula [formula diagram] wherein R is a base selected from the group consisting of [formula diagrams] wherein
>
> R1 is hydrogen, methyl, bromo, fluoro, chloro or iodo;
>
> R2 is hydroxy;
>
> R3 is hydrogen, bromo, chloro or iodo.

2. A nucleoside of claim 1 wherein the carbohydrate moiety is in the ribose form.

* * *

8. A nucleoside of claim 2 wherein the base is of the formula [formula diagram].

* * *

12. A nucleoside of claim 8 wherein R1 is hydrogen [i.e. qemcitabine].

13. A method of treating Herpes viral infections in mammals comprising administering to a mammal in need of such treatment an anti-Herpes viral effective amount of a compound of claim 1.

14. A pharmaceutical composition useful for treating Herpes viral infections comprising an anti-Herpes viral effective amount of a compound of claim 1 and a pharmaceutically-acceptable carrier, diluent or excipient therefor.

(emphasis added).

B. '826 Patent

The '826 Patent issued on November 7,1995 and is titled "METHOD OF TREATING TUMORS IN

MAMMALS WITH 2', 2'DIFLUORNUCLEOSIDES." The "ABSTRACT" reads "A method of treating susceptible neoplasms [cancers] in mammals comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of the compound of the formula [formula diagram] . . . ." The "SUMMARY OF THE INVENTION" states "The present invention provides a method of treating susceptible neoplasms [cancers] in mammals comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of the formula [formula diagram]." After giving seven examples of compounds, the '826 Patent continues:

> The term "pharmaceutically effective amount", as defined herein, refers to an appropriate amount of a compound of formula I which is capable of providing chemotherapy to mammals. The active compounds are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.1 to about 1200 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 50 mg/kg, in single or divided doses is preferred. . . . .

The pertinent claims of the '826 Patent read:

> 1. A method of treating susceptible neoplasms [cancers] in mammals comprising administering to a mammal in need of such

treatment a therapeutically effective amount of a compound of the formula [formula diagram] wherein:
R1 is hydrogen;
R2 is a base defined by one of the formulae [formula diagrams];
X is C-R4
R3 is hydrogen;
R4 is hydrogen, C1-C4 alkyl, bromo, fluoro, chloro or iodo; and the pharmaceutically-acceptable salts thereof.

2. The method of claim 1 in which the compound is 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-ifluororibose [i.e. gemcitabine] or a pharmaceutically acceptable salt thereof.

* * *

6. The method of claim 1 wherein the susceptible neoplasm [cancer] is selected from the group consisting of leukemias, sarcomas, carcinomas, and myelomas.

7. The method of claim 6 employing 1-(4 amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose [i.e. gemcitabine] or a pharmaceutically acceptable salt thereof.

(emphasis added).

On March 10, 1983, Lilly filed U.S. Patent Application No. 473,883 ("'883 Application"). On December 4, 1984, Lilly filed a "continuation-in-part" of the '883 Application, which ultimately lead to the '614 Patent. On December 4,1984, Lilly also filed U.S. Patent Application No. 677,783, which ultimately lead to the '826 Patent. Lilly advanced gemcitabine into clinical development as an anti-cancer agent on January 28, 1985. The '614 Patent issued on February 28, 1989, while the '826 Patent issued on November 7, 1995.

II. Argument

Sun Pharmaceuticals argues Lilly obtained the '614 Patent for the compound gemcitabine as an anti-viral and anti-cancer drug, then improperly extended its monopoly over the compound by obtaining the '826 Patent claiming a method of using gemcitabine to treat cancer. Sun Pharmaceuticals argues that, if a compound claim fails to adequately disclose the patentable bounds of the invention, the court may look to the patent specifications of both patents to determine if there is an overlap of claim scope. Sun Pharmaceuticals relies primarily on Pfizer, supra, and Geneva Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373 (Fed. Cir. 2003).

Lilly responds that Pfizer and Geneva are inapplicable because those cases involved initial compound patents that disclosed only a single utility in their specifications, and the subsequent patents claimed the earlier disclosed utility. Lilly argues that its earlier '614 Patent claimed the compound

gemcitabine and its essential utility as an anti-viral agent, and that the '826 patent claimed the new use of gemcitabine as an anti-cancer agent. Lilly asserts it disclosed the anti-cancer use in the '614 Patent specification to avert any "best mode" challenges to the validity of the '614 Patent, but relied on the anti-viral utility of gemcitabine to obtain the '614 Patent. Lilly maintains that, because the anti-cancer use of gemcitabine set forth in the '614 Patent specification was unnecessary to support the '614 Patent, the anti-cancer use was eligible for later patenting in the '826 Patent. Lilly argues that the court may not rely on the earlier patent specification as prior art to determine whether the later patent resulted in double patenting. Lilly maintains that In re Kaplan, 789 F.2d 1574 (Fed. Cir. 1986), is controlling.

III. Analysis

An obviousness-type double patenting analysis involves a two step process: (1) the court construes the claims of the earlier and later patents and determines their differences; and (2) the court determines whether those differences render the claims patentably distinct. Pfizer, 518 F.3d at 1363. Double patenting is an issue of law for the court to decide. Id.

Claim 12 of the '614 Patent claims the compound gemcitabine, a claim that is not dependent upon Claims 13 or 14, which claim, respectively, the method and use of treating Herpes viral infections. Claim 12 is a compound claim that, standing alone, does not adequately disclose the

patentable bounds of the invention. Therefore, this court may examine the specifications of both patents to determine any overlap in the claim scope for double patenting purposes. Geneva, 349 F.3d at 1385. Such was not the case in In re Kaplan, where a panel of the Federal Circuit ruled there was adequate support to determine the scope of a patent claim limitation "organic solvent" (as opposed to "organic solvents") from the claim language itself without resorting to the "mixed solvent" examples disclosed in the patent specification. In re Kaplan, 789 F.2d at 1575, 1580. The Kaplan court reasoned that the United States Trademark and Patenting Office ("PTO") erred in its double patenting analysis by treating the "mixed solvent" specification disclosure as prior art in rejecting a subsequent patent application claiming a process using a "solvent mixture." Id. Reversing the PTO's decision, the Kaplan court cited In re Vogel, 422 F.2d 438 (CCPA 1970) for the rule that treating a patent disclosure as prior art in performing an obviousness-type double patenting analysis "has repeatedly been held in our precedents to be impermissible." In re Kaplan, 789 F.2d at 1580.

Recently, a panel of the Federal Circuit explained the contours of Vogel when rejecting an argument that Kaplan forbids reading limitations from a patent specification into claims for purposes of conducting an obviousness-type double patenting analysis:

> .... While we stated in Kaplan that it is impermissible to treat a "patent

disclosure as though it were prior art" in a double patenting inquiry, we further reaffirmed the holding in In re Vogel, 57 C.C.P.A. 920, 422 F.2d 438 (CCPA 1970) that certain instances may exist where a patent's disclosure may be used. Kaplan, 789 F.2d at 1580. Indeed, our predecessor court stated that a patent's disclosure may be used to determine whether an application claim is merely an obvious variation of an invention claimed in a patent. Vogel, 422 F.2d at 441-42. The court stated that the disclosure may be used to learn the meaning of terns and in "interpreting the coverage of [a] claim." Id. at 441. It may also be used to answer the question whether claims merely define an obvious variation of what is earlier disclosed and claimed. The court stated that the disclosure "sets forth at least one tangible embodiment within the claim, and it is less difficult and more meaningful to judge whether [something] has been modified in an obvious manner." Id. at 442. The court further stated that "use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. § 103, since only the disclosure of the invention claimed in the patent may be examined." Id. As such, we conclude

> that the Board did not err in referring to the specification of the '987 Patent when it determined whether the claims were patentably distinct from the claims of the '687 Patent.

In re Basell Poliolefine Italia S.P.A., 547 F.3d 1371, 1378-79 (Fed. Cir. 2008).

Claim 12 of the '614 Patent fails to adequately describe the bounds of the claimed invention, and therefore, this court may use the specification disclosure in the '614 Patent, using gemcitabine for cancer chemotherapy treatment, to interpret the coverage of Claim 12. Id.; Geneva, 349 F.3d at 1385. Clearly, when properly considering the anti-cancer use of gemcitabine expressly disclosed in the '614 Patent specification, there is an overlap of Claim 12 of the '614 Patent and Claims 2, 6 and 7 of the '826 Patent. Indeed, there is an overlap of the identical "pharmaceutically effective amount" for anti-cancer treatment in the '614 Patent is repeated in the '826 Patent. A "claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use." Pfizer, Inc., 518 F.3d at 1363 (quoting Geneva, 349 F.3d at 1385-86). Construing Claim 12 of the earlier '612 Patent and Claims 2, 6 and 7 of the later '826 Patent, the court finds they are not patentably distinct as a matter of law. Pfizer, 518 F.3d at 1363.

> It would shock one's sense of justice if an inventor could receive a

> patent upon a composition of matter, setting out at length in the specification the useful purposes of such composition, manufacture and sell it to the public, and then prevent the public from making any beneficial use of such product by securing patents upon each of the uses to which it may be adapted.

Geneva, 349 F.3d at 1386 (quoting In re Byck, 48 F.2d 665, 668 (CCPA 1931)).

The court has limited its non-statutory double patenting analysis to a comparison of the Claims in the earlier '612 Patent to the Claims in the later '826 Patent, and does not rely on Lilly's motivations. Geneva, 349 F.3d at 1377 n.1. The timing of when Lilly discovered gemcitabine's uses for treating viral infections and treating cancer is irrelevant to the instant double patenting analysis. Lilly's assertion that it included the anti-cancer use of gemcitabine in the '612 Patent to avoid a later "best mode" challenge supports a conclusion that anti-cancer use was "contemplated by the inventor of carrying out [the] invention" set forth in Claim 12. See Pfizer, 518 F.3d at 1364 (quoting 35 U.S.C. § 112). While Lilly may be entitled to patent newly discovered uses of a previously disclosed compound, Ortho Pharm. Corp. v. Smith, 959 F.2d 936 (Fed. Cir. 1992); In re Maxwell, 578 F.2d 479 (CCPA 1951), it may not, as here, claim the same use of a compound in a later patent. Geneva, 349 F.3d at 1386. Lilly's argument that it was unnecessary to disclose the anti-cancer use in the '614 Patent because it relied on the anti-

viral utility to secure the '614 Patent does not displace the court's double patenting analysis. Although Lilly may not have been required to disclose the anti-cancer utility in the '614 Patent, it did make such a disclosure under circumstances which allow the court to interpret the coverage of Claim 12 using that disclosure. In re Basell Poliolefine, 547 F.3d at 1378 (quoting Vogel, 422 F.2d at 441-42). The court agrees with the reasoning in Boehringer Ingelheim International GMBH v. Barr Laboratories, Inc., 562 F.Supp.2d 619, 639 (D. Del. 2008), that, although Geneva and Pfizer involved single utility compounds, the rationale of Geneva and Pfizer are not limited to that circumstance. Construing Claim 12 of the '612 Patent along with the other Patent Claims, Lilly claimed two utilities for the compound gemcitabine - anti-viral and anti-cancer -and cannot now claim the same anti-cancer utility for the same compound. Boehringer, 562 F.Supp.2d at 639. Contrary to Lilly's argument, the court has not confused double patenting with "domination." See In re Kaplan, 789 F.2d at 1577. As opposed to a broad or "generic" claim, Claim 12 of the '612 Patent covers the specific anti-cancer use of gemcitabine as is also claimed in Claims 2, 6 and 7 of the '826 Patent. Based on clear and convincing evidence, these claims are not patentably distinct as a matter of law. Pfizer, 518 F.3d at 1363. Accordingly,

Sun Pharmaceuticals motion for partial summary judgment of invalidity of Eli Lilly's '826 Patent is hereby GRANTED to the extent the '826 Patent claims the method of treating susceptible

neoplasms [cancers] employing gemcitabine or a pharmaceutically acceptable salt thereof. Such claims are invalid as a matter of law under the doctrine of obviousness-type double patenting. Judgment shall enter in favor of Sun Pharmaceuticals on its claim that the '826 Patent is invalid. Eli Lilly's counterclaim of infringement of its '826 Patent is hereby DISMISSED.

SO ORDERED.

Dated: August 17, 2009

s/George Caram Steeh
GEORGE CARAM STEEH
UNITED STATES
DISTRICT JUDGE

Appendix C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,

Plaintiff,

vs.

SICOR PHARMACEUTICALS, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PARENTERAL MEDICINES, INC., — 1:06-cv-238-SEB-DML

Defendants.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This matter is before the Court for decision following a trial on the issues of validity, enforceability, and infringement of two patents held by Plaintiff Eli Lilly and Company ("Lilly"): United States Patent Nos. 4,808,614 ("the '614 patent") and 5,464,826 ("the '826 patent"). The '614 patent covers the compound gemcitabine, and the '826 patent covers the method of treating susceptible neoplasms in mammals with gemcitabine. Lilly markets gemcitabine for injection under the tradename GEMZAR®, which is approved for the treatment of

ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer. (DTX 39.)[1]

Lilly is the holder of approved New Drug Application No. 20-509 for the use of Gemzar® as a treatment for these cancers. In January 2006, Defendant Sicor Pharmaceuticals, Inc. ("Sicor") filed two Abbreviated New Drug Applications ("ANDAs") under the Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585 (popularly known as the Hatch-Waxman Act), with the Food and Drug Administration ("FDA") seeking approval to market generic versions of Lilly's gemcitabine product in two different dosage forms (200 mg and 1 g) prior to the expiration of the '614 and '826 patents. In August 2008, Defendant Teva Parenteral Medicines, Inc. ("Teva Parenteral")[2] filed a third ANDA seeking approval to market generic versions of gemcitabine in a third dosage form (2 g). Sicor's (and Teva Parenteral's) ANDAs included "paragraph IV certifications," pursuant to 21 U.S.C. § 355(j)(2)(A(vii)(IV), asserting that the claims of Lilly's '614 and '826 patents are invalid, unenforceable, or not infringed. As required by the Hatch-Waxman Act, Sicor and Teva Parenteral sent

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[1] When used in this order, "PTX" refers to Lilly's Trial exhibits; "DTX" refers to Defendants' trial exhibits; "LDX" refers to Lilly's demonstrative exhibits; and "TDX" refers to Defendants' demonstrative exhibits.

[2] After the present action was originally filed, Sicor Pharmaceuticals, Inc. changed its name to Teva Parenteral Medicines, Inc.

Lilly notice of these ANDA filings and paragraph IV certifications.

On February 15, 2006, after receiving notice of Sicor's ANDA filings and paragraph IV certification relating to the 200 mg and 1 g dosage forms, Lilly filed suit against Sicor and Teva USA alleging infringement of the '614 and '826 patents under 35 U.S.C. § 271 (e)(2)(A) and 35 U.S.C. § 271(b). Within forty-five days of receiving Teva Parenteral's notice relating to the 2 g dosage form, on September 26, 2008, Lilly filed suit against Teva Parenteral and Teva USA alleging infringement of the '614 and '826 patents. On January 15, 2009, the Court issued an order consolidating the two previously separate actions.

With the present action, Lilly seeks an order: (1) requiring the FDA to change the effective date of ANDA Nos. 77-961 and 77-983 until after the expiration of the '614 and '826 patents; (2) prohibiting the FDA from approving Teva Parenteral's ANDA No. 090644 prior to the expiration of the patents, in accordance with 35 U.S.C. § 271(e)(4)(A); and (3) enjoining Defendants from the commercial manufacture, use, offer to sell, sale, or importation of their gemcitabine products prior to the expiration of Lilly's exclusivity, in accordance with 35 U.S.C. § 271(e)(4)(B).

Defendants have stipulated that if Claim 12 of the '614 patent and Claim 7 of the '826 patent are valid and enforceable, then Defendants' actions

constitute infringement of those patents under 35 U.S.C. § 271(e)(2). (PTX 870, PTX 871).

Defendants challenge the validity of the '614 patent on the following grounds: anticipation under 35 U.S.C. § 102 and obviousness under 35 U.S.C. § 103. Defendants challenge the validity of the '826 patent on the following grounds: obviousness-type double patenting, anticipation under 35 U.S.C. § 102, obviousness under 35 U.S.C. § 103, and lack of enablement under 35 U.S.C. § 112. Defendants further assert that Lilly is collaterally estopped from asserting the '826 patent against them as a result of a prior determination of invalidity in a related case brought by another pharmaceutical company against Lilly in another district court.[3]

On the final day of trial, a post-trial briefing schedule was set for submission of the parties' proposed findings of fact and conclusions of law, post-trial briefs, and responses. These submissions were due on or before November 30, 2009. [Docket No. 339]. Having now considered the evidence adduced at trial as well as the parties' post-trial submissions, we hold, as detailed below, that: (1) the '614 patent is valid and enforceable and Defendants' proposed commercial gemcitabine product infringes claim 12 of that patent; and (2) although the '826 patent is valid and enforceable in all other regards,

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[3] That decision, Sun Pharm. Indus., Ltd. v. Eli Lilly & Co., 647 F.Supp.2d 820 (E.D. Mich. 2009), is currently awaiting a decision on appeal.

Lilly is collaterally estopped from defending against Defendants' claim of obviousness-type double patenting relating to that patent, pending a final determination on appeal.

Findings of Fact[4]

The Parties

Plaintiff Eli Lilly and Company ("Lilly") is an Indiana corporation with its principal place of business in Indianapolis, Indiana. Lilly is engaged in the business of research, development, manufacture, and sale of pharmaceutical products throughout the world.

Defendants Sicor Pharmaceuticals, Inc. ("Sicor"), now known as Teva Parenteral Medicines,

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[4] Defendants have moved to Admit into Evidence certain Deposition Designations and Exhibits Referenced Therein [Docket No. 355]. In order to streamline burdensome discovery, throughout pretrial and trial the parties negotiated agreements as to what evidence would be offered for admission. Outside of these agreements, on the final day of trial and thereafter, Defendants offered various additional exhibits for admission, (DTX F), but Lilly objects to the admission of certain of these submissions. DTX 55, 86, 149, 165, 845, and PTX 295-305, 307. Lilly does not object to the admission of the following: DTX 56, 145, 160, 180, 840, 843, 844, and 847. Defendants contend that Lilly's objections were belated, but the record makes clear that the late timing of the objections was the result of the late filing of the evidence by Defendants. It appears from the record that the parties did not, in fact, agree to admit this evidence. Moreover, this evidence is not, as Defendants contend, independently admissible. It is, by and large, unauthenticated or irrelevant, in particular because it lacks the support of introducing witness testimony. See Fed.R.Evid. 401, 602. Accordingly, Defendants' Motion to Admit is DENIED with regard to DTX 55, 86, 149, 165, 183, 845, and PTX 295-305, 307, but it is GRANTED as to DTX 56, 145,160, 180, 840, 843, 844, and 847.

Inc. ("Teva Parenteral"), and Teva Pharmaceuticals USA, Inc. ("Teva USA") (collectively "Defendants") are Delaware corporations. Defendants are engaged in the business of selling generic pharmaceutical products, which they distribute in Indiana and throughout the United States.[5]

The Patents-in-Suit

The '614 patent, issued on February 28, 1989 to Lilly, names Dr. Larry W. Hertel as the sole inventor. The '826 patent, issued on November 7, 1995 to Lilly, names Dr. Larry W. Hertel and Dr.

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[5] Defendants have also filed a Motion to Strike, or in the Alternative, Motion for Leave [Docket no 367], requesting that the Court strike Lilly's Counter-Findings of Fact and Counter-Conclusions of Law [Docket No 361], or in the alternative, requesting leave to file their own Counter-Findings and Conclusions At the close of trial, the Court established a schedule for the exchange of post-trial briefs. [Docket No 339]. That order required the parties to "file their opening briefs on or before Friday, November 6, 2009," and "their response briefs on or before Monday, November 30, 2009" Both parties filed proposed Findings of Fact and Conclusions of Law along with their opening briefs, despite the fact that the scheduling order made no mention of such Findings and Conclusions, thus demonstrating an understanding that, in the case at bar, such a filing would accompany any "brief" Nonetheless, only Lilly filed Findings and Conclusions in accompaniment with its Response Brief. Defendants have not explained their decision not to file Findings and Conclusions with their Response Brief, and it would be unfairly prejudicial to allow them, now, after Lilly's Counter-Findings, to file responsive Findings and Conclusions out of time Accordingly, Defendants' Motion to Strike is hereby DENIED

Gerald B. Grindey as joint inventors. Both patents are owned by Lilly.

The '614 patent discloses and claims a series of 2'2'-difluoronucleoside analogs, including gemcitabine. (DTX 1; D.I. 261 ¶ 23.) Claim 12, the only claim being asserted from the '614 patent, specifically claims the nucleoside analog gemcitabine. (Radtke 432:13-20.) The chemical name of gemcitabine appears as the eighth compound in a list of thirty-six potential 2'2'-difluoronucleosides. (DTX 1, col.3, II. 55-56.) The '614 patent claims priority to U.S. Patent Application Ser. No. 473,883 ("the '883 Application"), filed on March 10, 1983.

The specification of the '614 patent details the antiviral utility of this class of nucleoside analogs. It also contains one paragraph describing the later-discovered anticancer activity of this class of nucleosides and providing specific dosages. (PTX 1 at col. 17, II. 53-68.) The '883 Application, which was the original application in this patent, does not disclose any anticancer activity in the difluoronucleoside analogs. (Radtke 475:17-19.) The anticancer disclosure of the '614 patent was added by Lilly in a continuation-in-part application ("CIP"), Ser. No. 677,146, filed on December 4, 1984 ("1984 CIP Application"). (PTX 7 at 42; D.I. 261 ¶ 30.)

Also on December 4, 1984, the same day of the filing of the 1984 CIP Application related to the '614 patent, Lilly filed a completely separate patent application, which eventually issued as the '826

patent. The '826 patent claims the benefit, under 35 U.S.C. § 120, of a series of applications, the earliest having been filed on December 4, 1984, U.S. Patent Application Ser. No. 677,783 ("the '783 Application"). (PTX 9 at 3-46.)

The '826 patent discloses and claims methods of treating susceptible neoplasms with *gem*-difluoronucleosides, including gemcitabine. Claim 7 of the '826 patent, the only claim of that patent being asserted here, claims a method of treating susceptible neoplasms in mammals, where the susceptible neoplasm is selected from the group consisting of leukemias, sarcomas, carcinomas, and myelomas, and comprising the administration of a therapeutically effective amount of gemcitabine as treatment for human patients. (PTX 2 at col. 23, 1.42 - col. 24, 1.64; Green 220:25-221:6.)

Definition of Person of Ordinary Skill in the Art for the '614 Patent

At trial, Defendants' expert, Dr. Piet Herdewijn, and Lilly's expert, Katherine Radtke, testified that the person of ordinary skill in the art to which the '614 patent pertains would have a Ph.D. or equivalent degree in chemistry or the pharmaceutical sciences, with additional and considerable experience designing and synthesizing nucleoside analogs for biological purposes. (Radktke 432:25-433:15; Herdewijn 980:19-982:2.) Drs. Kathlyn Parker and Larry Overman held a similar view but did not include in their definition a particular expertise in nucleoside chemistry.

(Overman 599:6-17; Parker 1137:21-1138:10.) The definition of a person of ordinary skill in the art does not appear to be a matter of major dispute between the parties. We find that the definition must recognize the particular complexity of the science involved in the invention of the asserted claim, as well as the formative nature of the field of nucleoside synthesis at the time of the issuance of the patent.

Accordingly, based on the testimony of these experts, we find that a person of ordinary skill in the art for the '614 patent would have a Ph.D. in chemistry, postdoctoral training in nucleoside chemistry, and experience in the design and synthesis of nucleoside analogs for biological purposes.

Definition of a Person of Ordinary Skill in the Art for the '826 Patent

The invention of the '826 patent relied upon clinical trial experience, and Claim 7 of the '826 patent is directed to treating cancers, which are typically treated by clinical oncologists. As Defendants' expert, Dr. Kenneth Tew explained, in 1984, clinical oncologists administered cancer drugs to patients and were clinical trial investigators. (Tew 1273:9-19, 1277:17-20.) Because of the role of such experimentation in the development of the asserted claim, contrary to the opinion asserted by Defendants' experts that clinical oncologist expertise would not be part of the "ordinary" knowledge in the art, the definition of a person of ordinary skill in the art must consider the role of designing,

implementing, and conducting clinical trials necessary for a complete understanding of the skill required in this field. (Green 222:2-16.) Furthermore, Lilly's expert, Dr. Mark Green, testified that the '826 patent, which is a method of use patent, does not require medicinal chemistry.[6] (Green 222:17-21.)

Accordingly, we hold that, for the '826 patent, a person of ordinary skill in the art would have a medical degree (M.D.) or a Ph.D. degree in biology, pharmacology, or a similar degree in a related field of science, and would have experience in developing chemotherapeutic agents for the treatment of cancer. That person would have knowledge encompassing the design, implementation, and execution of clinical trials. (Green 221:21-222:10.)

Gemcitabine and Nucleoside Analogs Generally

The Food and Drug Administration ("FDA") has approved gemcitabine, sold by Lilly as Gemzar®, for use in treating patients with neoplasms, including pancreatic, lung, ovarian, and breast cancers. (PTX 443 at 10-11.) Gemcitabine has been used to treat approximately 1.5 million patients worldwide since its first approval in 1996. (D.I. 287,

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[6] We note that the analysis regarding the '826 patent would be the same if the definition of a person of ordinary skill in the art as proposed by Drs. Rustum or Herdewijn, as opposed to the standard proposed by Drs. Green and Radtke, was adopted. (See Shewach 747:14-18; Rustum 1512:13-20.)

Grabowski Rep. ¶ 45.) Currently, gemcitabine is the primary therapy given to patients with advanced pancreatic cancer, as experimental data indicates that it offers improved one-year survival nine times better than the previous standard of care. (Green 200:11-201:4; PTX 436 at 2403.)

Gemcitabine is a "nucleoside analog," or a modified version of a class of compounds called nucleosides, which are the building blocks of DNA. (Shewach 770:3-14; LDX 8.24.) Nucleosides consist of a 5-member "sugar" ring joined to a "base." Radtke 426:14-16; LDX 7.2.) By convention, the atoms at each of the corners of the base are numbered 1 through 6, and the carbon atoms at each corner of the sugar are numbered 1' ("1 prime") through 5'. Gemcitabine differs structurally from the natural nucleoside 2'-deoxycytidine in that it has twin fluroine atoms at the C-2' position of the sugar (hence, the "gem" in its name, which stems from "geminal," for twin). (Radtke 433:23-434:4.)

Nucleoside analogs can be used as anticancer or antiviral agents because they are similar enough in structure to naturally occurring nucleosides that cells are tricked into accepting them, but are different enough to disrupt cell functioning and replication once inside the cell. (Rustum 1537:6-1538:6.) Because of these attributes, since at least the 1960s, chemists specializing in nucleosides have explored the implementation of structural changes to naturally occurring nucleosides in an effort to produce nucleoside analogs with therapeutic properties. (Radtke 441:15-24; Shewach 792:19-793:2; PTX-602.) This process and the results it

engenders have been regarded as highly unpredictable; as one leading researcher stated in a 1973 review article, "[O]nly Zeus sitting on top of Mount Olympus could predict which modifications would produce clinically effective antiviral agents. Unfortunately, we poor mortals are not privy to such knowledge." (Radtke 430:15-431:15; PTX 647 at 881: see also PTX 692 at 3-5).

Even today, scientists in the field regard nucleoside analog design for therapeutic anticancer purposes as very unpredictable. (Radtke 431:12-432:5.) This unpredictability stems from the profound change in biological properties that can be created by minor changes in the structure of a nucleoside compound. Slight structural modification can drastically alter the biological activity of nucleoside analogs. This is the result of the effect structural modification typically has on the three-dimensional shape of the compound, which alters the analog's ability to interact with biologically significant enzymes. (Radtke 427:15-430:14.) An example given in this litigation was that the building blocks of RNA and DNA, two compounds that are processed by the human body in remarkably different ways, differ physically in only one respect: that the RNA nucleosides have a hydroxyl group (OH) at the C-2' position, whereas DNA nucleosides do not. (Radtke 427:15-428:5; LDX 7.3.)

The key modification in gemcitabine involves the element fluorine. In the early 1980s, fluorine chemistry as applied to the nucleoside field was relatively new, and little was known about how one

might synthesize difluorinated nucleosides. (Overman 596:7-601:17; 615:13-616:25.) Indeed, years after the invention of gemcitabine, Dr. Herdewijn wrote that "the synthesis of fluorinated nucleosides is still a difficult task." (PTX 688 at 67.) Furthermore, the properties of fluorine, which is the most electronegative atom of all known elements,[7] are known to lead to particularly unpredictable results, with corresponding unpredictable effects on biological activity. (Overman 615:13-616:1; Radtke 434:12-20.) Because of this electronegative potency, a geminal fluorine substitution, like the one in gemcitabine, was a particularly unpredictable addition to nucleoside analogs. (Bergstrom 935:15-936:22; PTX 533 at Bergstrom 21; see also Rustum 1605:14-22.)[8] This unpredictability remained even after Lilly's development of gemcitabine; as Defendants' expert, Dr. Herdewijn wrote in a 1989 review article, "[I]t seems very difficult to predict [a] molecule's biological behaviour when a C-H or a C-OH has been displaced by a C-F group." (PTX 688 at 66; Herdewijn 1097:2-13.)

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[7] Dr. Radtke explained that fluorine's powerful electronegtivity works like a magnet, deactivating the carbon atoms on either side of the carbon to which it is attached. (Radtke 434.5-435:2)

[8] Drs. Radtke, Herdewijn, and Rustum agreed that the prior art did not contain any examples of biologically active nucleoside analogs with geminal substitutions at the C-2' position, let alone a difluoro substitution at the C-2' position. (Radtke 435:15-25, 437:18-438:6; Herdewijn 1092:15-19; Rustum 1605:2-11.)

The unpredictability in this area of chemistry is, in large part, the reason that gemcitabine remains the primary treatment for particularly intractable neoplasms. Prior to Lilly's synthesis of this compound, no other research team had synthesized a nucleoside analog with geminal fluorine atoms. (Radtke 473:12-474:5.). Furthermore, between that synthesis and the year 2000, roughly forty similar nucleoside analogs (with geminal fluorine atoms at the 2'-position) had been reported, yet none had proved effective for treating cancer in humans. (Radtke 528:14-529:6; PTX 620 at 87-88.) More broadly, out of nearly 300,000 compounds that had been evaluated as anticancer agents by 1979, shortly before Lilly's synthesis of gemcitabine, only forty were deemed useful in treating neoplasms. (Shewach 744:8-745:8; PTX 692 at 3.)[9]

Nucleoside Analogs in the Prior Art

Defendants point to three compounds they contend were contained in the prior art and were significant to the development of gemcitabine: *Ara-C*, which has an OH group "up" at the 2' position; 2'-

[9] Dr. Youcef Rustum, an expert witness offered by Defendants, testified with regard to anticancer agent development that "the success rate is very low. So out of 10,000 or 20,000 compounds tested here and there, you may have one compound make it to the market." (Rustum 1576:7-9.)

F-*ara*-C, which has one fluorine "down" at the 2' position; and 2'-F-cytidine, which has one fluorine "down" at the 2' position. These three, according to Defendants, presaged Lilly's discovery.

In the 1970s, the first of these compounds, *Ara*-C, was a widely used anticancer drug. (Bobek 1300:18-13-1:3.) Although it was relatively effective, the compound was rapidly deactivated in the body by a process called "deamination." (Bobek 1301:8-16.) Because of problems stemming from this lack of effectiveness, researchers at the Fox Laboratory at Memorial Sloan-Kettering Cancer Center ("Sloan-Kettering" or "Fox Laboratory") and elsewhere had undertaken efforts to improve on *Ara*-C.

The two fluorinated nucleoside analogs, 2'-F-*ara* C and 2' F-cytidine, had been synthesized in the 1960s by Sloan-Kettering. (Radtke 441:15-442:17; Shewach 750:20-751:6.) But neither compound was reported in the prior art to have been advanced to testing in animals, as compounds with promise for medical activity typically are. (Shewach 752:25-753:10.) Nor was either considered a lead compound for further exploration in the late 1970s and early 1980s. (Radtke 440:22-441:6.)

2'-F-cytidine was first reported in 1967 and found to be twenty times less cytotoxic *in vitro* than *Ara*-C. (Radtke 441:15-24; PTX 602.) The fact that 2'-F-cytidine did not effectively inhibit DNA synthesis in intact cells indicated that it also did not

significantly inhibit the enzyme ribonucleotide reductase ("RNR")[10] *in vivo*. Moreover, although this nucleoside analog was discovered in 1967, Fox Laboratory never tested it for biological activity in animals or in the clinic, nor did any other laboratory so test it. (Shewach 752:25-753:10; Radtke 448:2-20.)

In 1970, researchers at Sloan-Kettering reported that they had synthesized 2'-F-*ara*-C. (Radtke 448:21-449:14; PTX 603.) However, similar to 2'-F-cytidine, this analog posed no improvement on the *in vitro* cytotoxicity of *Ara*-C, and the prior art reported no *in vivo* activity for 2-F-*ara*-C. (Radtke 454:13-18.)[11]

In contrast to these two compounds, which the prior art largely deemed of low antiviral and anticancer activity, two nucleoside analogs referred to as FIAC and FMAU were identified by researchers as the "most potent and selective" of the fluorinated Sloan-Kettering analogs. (Radtke

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[10] RNR is critical to DNA replication and is essential for cell proliferation. If RNR is inhibited, DNA cannot be replicated and cell proliferation is prevented. (Rustum 1529:9-1530:9.)

[11] A subsequent publication reported that Fox Laboratory had, in fact, tested 2'-F-*ara*-C *in vivo* but that the compound showed "little antitumor activity." (Shewach 752:25-753; Rustum 1602:3-1603:15 PTX 620 at 90.)

454:19-456:9; PTX 584 at 30.)[12] Dr. Herdewijn, Defendants' expert, noted in a 1989 review that FIAC and FMAU were "important" nucleoside analogs for further study, omitting any mention of 2'-F-cytidine or 2'-F-*ara*-C. That the FIAC and FMAU compounds were more prominent in the prior art than 2'-F-cytidine and 2'-F-*ara*-C is further supported by a presentation prepared by Dr. Donald Bergstrom in 1980, which mentioned neither 2'-F-*ara*-C and 2'-F-cytidine but did describe FIAC. (PTX-541 at Bergstrom 3257.)

In addition to providing information regarding the properties of these compounds, the research referenced in the prior art indicated to those skilled in the art that a nucleoside analog's *in vitro* cytotoxicity does not necessarily correlate with *in vivo* anticancer activity. (Shewach 795:23-797:7; PTX 725 at 1163; Rustum 1586:13-15.) Thus, any *in vitro* data reported for 2'-F-*ara*-C and 2'-F-cytidine was not necessarily indicative of how those compounds would act *in vivo*. (Rustum 1583:25-1584:4.) As the prior art revealed with considerable clarity, because viruses produce different enzymes than mammalian cancer cells, (Herdewijn 1105:6-15; Shewach 857:14-21; PTX 937 at 486), not all molecules exhibiting antiviral activity also have anticancer activity.

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[12] These compounds progressed to studies in animals and were promising enough at that time to draw considerable attention from Lilly. (PTX 584 at 27.)

Dr. Miroslav Bobek's Attempts to Synthesize Gemcitabine

Dr. Miroslav Bobek, now a retired medicinal chemist, spent the majority of his career developing modified nucleosides for anticancer purposes at Roswell Park in Buffalo, New York. (Bobek 1299:1-7.) In connection with this work, in June 1977, Dr. Bobek submitted a manuscript to *Tetrahedron Letters* setting forth proposed synthetic routes for making gemdifluorosaccharides, including a method used in his laboratory for making an intermediate of gemcitabine. (DTX 95; Bobek 1322:6-1323:8, DTX 873 at SICOR/TEVA-Bobek 472.) In March 1978, Dr. Bobek carried out a series of chemical reactions with the intention of creating gemcitabine, but he never succeeded in synthesizing the compound. (Bobek 1324:9-1330:10.)

Dr. Bobek reports that he publicly presented his work on gemcitabine in the 1970s during at least one seminar held at Roswell Park. (Bobek 1317:8-1319:25; DTX 220 at SICOR/TEVA-Bobek 133.) During that time period, Dr. Gerald Grindey, a named inventor on the '826 patent, was a colleague in the same department as Dr. Bobek. (DTX 78.) Dr. Grindey left his position with Roswell Park in December 1980 to join Lilly.[13]

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[13] As discussed in the Conclusions of Law, Defendants attempted to show at trial that Dr. Grindey, not Dr. Hertel, originally proposed using gemcitabine as an antitumor agent at Lilly and that he did so based on knowledge gained from Dr. Bobek.

Dr. Bobek's laboratory notebook contains a series of attempted reactions leading to an intermediate of gemcitabine, but none of them resulted, even hypothetically, in gemcitabine itself. (Bobek 1324:9-23; 1325:11-19; PTX 508 at 61.) His first relevant experiment, in which he attempted to make a difluoronucleoside using DAST,[14] failed. (Bobek 1358:7-9, 1359:8-9; Radtke 459:12-436:3; PTX 492.) Similarly, an alternative synthesis which started with a 6-member ring sugar that was reported in his grant application was reported to have failed. (PTX 499 at Bobek 202; PTX 500 at Bobek 154.)

Although Dr. Bobek claimed at trial that his experiments and proposed reactions were capable of producing gemcitabine, no other evidence in the record supports this claim. None of Defendants' experts testified that Dr. Bobek actually synthesized gemcitabine, or even that his synthetic route was capable of doing so. Moreover, experimental evidence demonstrated clearly that the synthetic route purportedly used by Dr. Bobek could not have produced gemcitabine. (Radtke 485:11-25; Overman 623:13-625:5; PTX 509; PTX 516.) Eventually, Dr. Bobek abandoned his attempts to synthesize the compound and focused instead on the pursuit of

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[14] DAST is a fluorinating agent, which as its name and the evidence provided by both parties' experts suggests, is a compound utilized in fluorine substitution. (DTX 95, Herdewijn 1032:16-22, Overman 619:5-10.)

other nucleoside analogs. (Bobek 1330:20-25; 1394:1-6.)

Dr. Donald Bergstrom's Attempts to Synthesize Gemcitabine

Dr. Donald Bergstrom, who was, prior to March 1983, a professor at the University of North Dakota and is now a professor at Purdue University, also had proposed the synthesis of difluoronucleosides. (DTX 265; DTX 206 at SICOR/TEVA-Bergstrom 22.) However, like Dr. Bobek, Dr. Bergstrom also never successfully produced gemcitabine. (Bergstrom 920:18-20.)

Dr. Bergstrom utilized several routes in attempting to synthesize 2',2'-difluoro-2'-deoxynucleosides. (Bergstrom 946:23-948:5; PTX 534.) He set forth his rationale for conducting these experiments in grant applications that he submitted to the National Institute of Health ("NIH") in May and October of 1982. (DTX 206 at SICOR/TEVA-Bergstrom 4, 22; DTX 207 at SICOR/TEVA-Bergstrom 47. 63.) His May 1982 grant application stated that "of particular interest to us is the 2'-deoxy-2',2'-difluoro substitution pattern." (DTX 206 at SICOR/TEVA-Bergstrom22.)

Based on this work, Dr. Bergstrom submitted an abstract entitled "Synthesis of Gem-Difluoro Substituted Nucleoside Analogs" (the "Bergstrom Abstract") to the American Chemical Society before a March 1983 meeting at which he was scheduled to make a presentation ("1983 ACS Meeting"). (DTX

265; DTX 264 at 41.) The Bergstrom Abstract, a copy of which Dr. Hertel received on or about March 1, 1983, (PTX 6 at 52), reported that Dr. Bergstrom's laboratory was attempting to synthesize 2' and 3' gemdifluoronucleosides, which Dr. Bergstrom anticipated would include gemcitabine. (DTX 265.)[15] Dr. Bergstrom publicly presented his research attempts at the 1983 ACS Meeting, and the slides he used in that presentation depicted the structure of gemcitabine. (Bergstrom 914:6-9, 915:1-917:3; DTX 455.)

Although Dr. Bergstrom made a 3',3'-gemdifluoronucleoside, he never successfully prepared the compound gemcitabine. (Radtke 466:13-467:15; PTX 518; Bergstrom 954:5-14.) Furthermore, while Dr. Bergstrom proposed several different *de novo* synthetic routes, he did not utilize a Reformatsky reaction, the route utilized by Dr. Hertel to synthesize gemcitabine. Because Dr. Bergstrom was never able to synthesize either a 2',2'-difluoronucleoside or the precursor of gemcitabine, he eventually abandoned his efforts and concentrated instead on other nucleoside analogs. (Bergstrom 923:11-19, 921:25-923:7; PTX 534 at Bergstrom 68-69.)

Merrell Dow's Synthesis of Gemcitabine

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[15] Lilly informed the PTO that the Bergstrom Abstract "suggests 2',2'-difluoro structures as well." (PTX 6 at 52.)

Dr. Robert Farr and Dr. Brian Metcalf at Merrell Dow Pharmaceuticals, Inc. also sought to synthesize gem-difluoronucleosides. (DTX 851, Metcalf Dep. Tr. 11:16-12:6, 16:14-18; Radtke 512:20-513:3.) Dr. Metcalf's involvement centered largely on envisioning the use of a nucleoside having a 2' gem-difluoro sugar coupled to a natural base to inhibit RNR, which he hoped would prove to have an anticancer utility. (DTX 151-153; DTX 851, Metcalf Dep. Tr. 33:11-14, 20-21, 23-4, 34:2-10; Farr Dep. Tr. 25:6-9, 11-13.)[16] Dr. Farr, who worked under Dr. Metcalf's supervision until Dr. Metcalf's departure from Merrell Dow in December 1983, proposed a synthetic route that included a Reformatsky reaction and a Sharpless epoxidation to produce the compound. However, this route also proved unsuccessful. (PTX 552 at SA 2212-13; PTX 554 at SA 2200; Radtke 514:17-515:25, 516:3-5.)

Dr. Farr next attempted an approach derived from an article published in 1984, which also proved unsuccessful. (PTX 557 at SA 2182; PTX 566; PTX 6; Farr Dep. 47:18-51:17.) Dr. Farr did not, in fact, succeed in producing gemcitabine until, at the earliest, December 1984, and he did not test it for anticancer utility until May 1985, after a review of Dr. Hertel's synthetic method reported in Lilly's 1984 published British patent application. (DTX 162 at SA 2861, 2865; PTX 16; PTX 557 at SA 2185; PTX

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[16] Dr. Metcalf also conceived, generally, of a proposed structure for the anticancer agent he hoped Merrell Dow would produce. (DTX-151 at SA 2208.)

568, 17:47-51, 18:49-30:39; PTX 16, 4:43-9:47; Farr. Dep. 59:12-17, 59:20-60:2, 91:19-93:25.) Merrell Dow filed a patent application on the use of gemcitabine as an antitumor agent in July 1985. (DTX 895.)

Lilly's Invention of Gemcitabine and Discovery of its Utilities

I. The '614 Patent: Difluoronucleosides and Antiviral Utility

Lilly's interest in developing nucleoside analogs as antiviral agents manifested itself in the early 1980s, when Lilly sought to obtain rights from Sloan-Kettering to develop FIAC and FMAU for antiviral utility. (Hertel 270:16-25, 271:23-272:15; PTX 22 at GM 197972.) Lilly was, however, unsuccessful in obtaining a license to these compounds. (Pearce 146:21-24, 147:13-14.) Thereafter, Dr. Larry Hertel, an employee at Lilly, became responsible for searching out ways to synthesize monofluorinated nucleoside analogs like FIAC and FMAU, in order to provide quantities of the compounds for further testing. (Hertel 271:1-13.).

Dr. Hertel proposed a new strategy called "*de novo*" or "total" synthesis as a method of producing the compounds, despite the fact that this method had been dismissed by other researchers as a "method of limited usefulness." (Hertel 283:13-19, 352:25-353:24; PTX 19 at GM 153104; PTX 22 at GM 197983-84; PTX 648 at 237.) At this time, he also proposed the preparation of a "key intermediate" he

believed could be used to make geminal difluoronucleosides with two fluorine atoms at the C-2' position, hoping that these new compounds would produce antiviral utility. (Hertel 273:13-275:21, PTX 19 at GM 153127; PTX 22 at GM 197985-86.)

Dr. Hertel's synthesis of geminal difluoronucleosides was not immediately successful, as many of his attempted synthetic methods failed and he encountered unexpected impediments during his research. (Hertel 285:25-287:10; PTX 24 at GM 198006-08.) Included in his failed attempts were an intensive effort to synthesize the compounds using a "Sharpless epoxidation." (Hertel 282:17-284-14. 287:18-288:8). Overall, Dr. Hertel spent four months (May 1981 to September 1981) attempting to prepare the necessary Sharpless intermediate. Dr. Hertel tried at least four categories of reaction to accomplish this goal, and he contacted Dr. Sharpless, a Nobel Prize-winning synthetic organic chemist, and Dr. Evans, another prominent synthetic organic chemist, for advice. (Hertel 284:12-14; 287:18-20.) Both of those prominent chemists believed the route Dr. Hertel proposed would be successful. (Hertel 283:4-284:11, 287:11-289:14; PTX-19 at GM 153104.) Nonetheless, all of these attempts failed. (Hertel 285:25-292:13, 302:24-303:8.) During the time period from July to December 1981, Dr. Hertel shifted his focus by attempting a more direct synthetic strategy using the DAST reagent. (PTX 24 at 199; Hertel 301:15-302:23.) Like the previous strategy, this attempt also failed. (Hertel 302:9-10.)

In the face of these setbacks, Dr. Hertel proposed a different *de novo* approach using a "Reformatsky" reaction. Applying this method, in September 1981, he succeeded in synthesizing the carbon backbone of the 2' gem-difluoro sugar, which was a precursor of gemcitabine. (Hertel 292:14-294:9, DTX-126 at 57; PTX 24 at 193.)

According to Dr. Hertel, despite this success, the process thereafter was quite rigorous and complex, consistent with what was known in the prior art about the unpredictability of fluorination:

> And what we discovered very rapidly is once you introduce fluorine into an organic molecule, it significantly alters the chemistry of that molecule by deactivating some centers or activating others to reactions in that in a normal organic molecule wouldn't be involved. And so essentially, you had to kind of learn organic chemistry all over again when you started working with a fluorinated organic.

(Hertel 297:13-20.) Dr. Hertel's laboratory initially attempted to couple the sugar intermediate he had produced with the base thymine, rather than cytosine, the base in gemcitabine. (DTX 129, 130, 421; PTX 19, 24, 26, 31.)

In June 1982, after many more attempts, the laboratory successfully synthesized the first difluoronucleoside in the series, 2',2'-

difluorothymidine. (Hertel 311:17-313:4; PTX 26 at 162, 164.) Gemcitabine was the second nucleoside analog made by Dr. Hotel's laboratory. (PTX 31 at GM 161073, 161075; Hertel 327:17-329:7.) Lilly later tested Dr. Hotel's difluoronucleosides, and, by June 15, 1982, the first 2',2'-difluoronucleoside had exhibited promising activity against viruses. (Hertel 316:1 -319:7; PTX 26 at GM 162163; PTX 228.) Dr. Hertel's difluoronucleosides demonstrated antiviral activity against both DNA and RNA viruses. (Hertel 316:1-319:7, 330:8-24; PTX 181 at GM 152170; PTX 228; PTX 229; PTX 242.)

On March 10, 1983, Lilly filed its original patent application related to Dr. Hertel's difluoronucleosides, the '883 application, which listed these compounds, including the first documented reference to gemcitabine. The '883 application also described the method of manufacturing the compounds and explained their antiviral utility. (PTX 6 at 9.) Claim 12 of the patent that issued from this original application, the '614 patent, covers the nucleoside gemcitabine. (Radtke 423:13-20.)[17]

The '614 patent is entitled "Difluoro Antivirals and Intermediate Therefor." (PTX 1.) Consistent

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[17] The following references are cited on the face of the '614 patent: Watamane (1979 (PTX-587), U.S Patent No. 4,211,733 ("'773 patent"); the Bergstrom Abstract (PTX-518), Adamson (1971) (PTX-581); Fox (1981) (PTX-584); and Penglis (1981) (PTX-648).

with its title, the patent is directed primarily to using the listed difluoronucleosides as antiviral agents. See id. However, the patent also contains a paragraph describing the later-discovered anticancer activity of these compounds. This paragraph was added on the same day that Lilly filed the original patent application ultimately leading to the '826 patent, the second patent-in-suit. Specifically, on December 4, 1984, Lilly filed the 1984 CIP Application, a continuation-in-part the '883 application that ultimately led to the issuance of the '614 patent. (PTX 7.) In accordance with the "best mode" requirement of 35 U.S.C. § 112, Lilly included in the 1984 CIP Application one paragraph discussing the later-discovered anticancer activity of the difluoronucleosides. That later discovery as contained in a separate patent application and discussed immediately below led to the issuance of the '826 patent.

II. The '826 Patent: Gemcitabine's Anticancer Utility

Soon after he had successfully synthesized difluoronucleosides and had them tested for antiviral activity, Dr. Hertel submitted several of the compounds to Dr. Gerald Grindey, a Senior Research Scientist at Lilly, who was seeking compounds for testing in anticancer screens. (Hertel 330:25-331:20, 332:25-333:10; PTX 31 at 195; Pearce 158:9-15.)

Although few of the compounds demonstrated anticancer utility in the tests conducted by Dr. Grindey, gemcitabine exhibited significant

cytotoxicity, orders of magnitude better than the other difluoronucleosides. (PTX 173 at GM 154671; PTX 181 at GM 152170.) Dr. Grindey described it as "singular among all difluoronucleosides tested to date." (Pearce 100:9-19; PTX 179 at GM 258388.) Dr. Grindey's laboratory first screened gemcitabine for cytotoxicity in human cancer cells on November 1, 1983. (PTX 118 at GM 157170; Hertel 334:1-21.) The compound was first tested *in vivo* on leukemia beginning on February 22, 1984. (Pearce 90:16-91:9; PTX 126.) Gemcitabine showed a very significant improvement in the life span of mice, used in the *in vivo* testing, over a very broad range of doses in a test initiated on May 9, 1984 and completed on June 6, 1984. (PTX 173 at GM 154671; Pearce 89:20-90:8, 91:22-92:5; PTX 131.)

By August 13, 1984, Dr. Grindey's laboratory had collected and reviewed nearly all of the antitumor data for gemcitabine that appears in the '826 patent. (PTX 2; PTX 131; PTX 132; PTX 129; PTX 136; PTX 128; PTX 134; Pearce 90:16-92:5, 93:20-95:3, 104:20-105:6.) Ultimately, Dr. Grindey's *in vivo* testing of gemcitabine's antitumor activity demonstrated the compound's activity against a wide array of solid tumors, a "very unusual feature" for a nucleoside analog and the "broadest spectrum of any agent ever tested at Lilly." (PTX 173 at GM 154672; PTX 179 at GM 258390; Pearce 101:15-102:6.)

On December 4, 1984, based on Dr. Grindey's findings, Lilly filed a patent application on their discovery of the anticancer utility of gemcitabine, naming Drs. Grindey and Hertel as inventors. This

filing came more than twenty months after the filing of '883 application, which was the original application of the '614 patent. The '826 patent, which resulted from the '783 application, was entitled "Method of Treating Tumors in Mammals with 2',2'-Difluoronucleosides" and contained *in vitro* and *in vivo* experimental data supporting the method of using various difluoronucleosides, including gemcitabine, to treat susceptible neoplasms in mammals. (PTX 2.) Claim 7 of the '826 patent is limited to using gemcitabine to treat different types of cancer. (PTX 2; Green 220:25-221:6.)[18]

The goal of the '826 patent is to treat cancer in humans. (Tew 1273:9-12.) One of ordinary skill in the art reviewing the patent and its prosecution history, along with the relevant art in 1984, would know that the claimed invention dealt with the treatment of cancer in human patients, not all mammals.[19] The '826 patent provides extensive

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[18] The following references are cited on the face of the '826 patent: Brox (1975) (PTX-593), Adamson (1971) (PTX-581), and Goodman and Gilman (1980) (PTX-473)

[19] During the prosecution of this patent, Lilly reported mouse tumor model data, which led Defendants' expert, Dr. Tew, to conclude that the patent was not enabled because determining all neoplasms susceptible to gemcitabine in all mammals would require "undue experimentation." (Tew 1251:23-1252:17.) This opinion is belied by the nature, use, and development of the patent. As Dr. Pearce testified, it was standard practice to investigate potential anticancer agents in mouse tumor models. (Pearce 80:19-81:10). The fact that Lilly so tested gemcitabine is not an indicator that it intended to use

(continued...)

information as to how to make and use the claimed invention. (PTX 2.) It describes the synthesis of gemcitabine and demonstrates the compound's cytotoxic activity *in vitro* and *in vivo*. Using standard mouse tumor model data, the patent discloses a broad range of activity, which would have led a person of ordinary skill in the art using valid methods and appropriate models to expect gemcitabine to have broad efficacy in humans against a variety of cancers. (Green 223:11-16.) Further, the patent discloses that physicians will be responsible for determining therapeutic doses of gemcitabine in humans. (PTX 2 at col. 16,ll. 2-8; Green 220:6-22.)

In order to determine the types of cancers for which gemcitabine would demonstrate efficacy in humans, one skilled in the art would have understood that the compound should be tested in the clinic in phase I and/or phase II studies, which were routine to a person of ordinary skill in 1984. (Green 223:17-25, 258:25-259:7; Tew 1254:1-4.) As Defendants' expert, Dr. Tew, explained, phase I, II, and III clinical trials are "what pharmacologists and clinical oncologists do." (Tew 1286:6-11.) Undertaking this experimentation would have been relatively straightforward to a person of ordinary

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(...continued)
gemcitabine to treat mice with cancer, let alone any mammal other than humans with cancer. It merely reflects the fact that Lilly was following standard procedure for the development of a drug to be used in humans

skill in the art because the approach to designing clinical trials was known and well documented. (Tew 1284:9-25, 1285:1-17.)

III. The Unexpected Properties of Gemcitabine

Gemcitabine exhibited a number of properties that would have been unexpected to the person of ordinary skill in the art, including a unique mechanism of action, broad activity in treating susceptible neoplasms, and increased survival and higher clinical benefit response in the treatment of pancreatic cancer when compared to 5-fluorouracil ("5-FU").[20]

A number of gemcitabine's mechanistic properties would have been unexpected, such as greater transport into cells and higher accumulation and retention inside cells, both of which provide an improved capacity to kill cancer cells over *Ara*-C. (Shewach 754:4-755:14, 759:12-763:18, 764:2-6; PTX 695 at 4028, PTX 696 at 100; LDX 8.7-8.8, 8.13-8.16.) Gemcitabine also proved to have superior effects on DNA synthesis, increased incorporation into DNA, and remarkable ability to inactivate the enzyme RNR. (Shewach 754:4-755:14, 763:19-768:21, 769:15-781:11; PTX 712 at 6110, 6116; PTX 705 at 567, 571; PTX 703 at 3220; LDX 8.21-8.29.)

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[20] At the time Lilly was developing gemcitabine, 5-fluorouracil was the accepted standard of care for advanced pancreatic cancer. (Pearce 116:1-10.)

As a result of these properties, gemcitabine exhibited unprecedented activity against a broad spectrum of cancers. (Shewach 754:21-23.) Gemcitabine's activity against tumors, including solid tumors, was unexpected in view of and in comparison to the compounds in the prior art. (Pearce 95:22-96:14; Green 178:16-22, 217:5-19.) Furthermore, at least one study[21] concluded that patients with advanced pancreatic cancer treated with gemcitabine alone demonstrated a statistically significant, unexpected survival advantage and higher clinical benefit response when compared to those treated with 5-FU. (Green 178:5-15, 200:11-201:4; PTX 436 at 2403, 2406, 2409, 2412; LDX 5.12-5.13.)[22]

IV. Gemcitabine's Impact on the Market

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[21] The FDA approved gemcitabine for the treatment of patients with pancreatic cancer based on the results of a multicenter, randomized, blinded, and controlled phase III study, identified at Lilly as B9E-MC-JHAY ("the JHAY study") (PTX 274.) The results of the JHAY study were published in Burris et al, Journal of Clinical Oncology 15(6):2403-13 (1997) (PTX 436.)

[22] Defendants' expert Dr Isacoff criticizes the results of this study, (e.g. Isacoff 1433:5-7), but the record of evidence at trial, including other expert testimony, convinces the Court of the soundness of the study. (Pearce 115:12-21, 119:8-20; Green 203:8-204:3, 206:15-207:8, 227:5-10; PTX 480 at PANC-D, MS-14; LDX 14.4-14.5.) Of particular relevance is the fact that Dr Isacoff himself prescribes gemcitabine to half of his patients diagnosed with advanced pancreatic cancer. (Isacoff 1462:13-16.)

For decades prior to the development of gemcitabine, researchers experienced significant difficulty developing effective treatments for solid tumors, despite success in treating other forms of cancer. (PTX 460 at 12; PTX 461 at IV-50; Rustum 1581:15-21; Pearce 81:15-82:1 .)[23] During this period, patients suffering from advanced pancreatic cancer consistently faced a particularly negative prognosis because no chemotherapy was available that was effective as a treatment. (Green 183:19-184:5; PTX 452 at 2061.) Prior to gemcitabine, only two drugs had been approved by the FDA for use in patients with this disease: 5-FU and mitomycin. (Green 182:25-183:18.) 5-FU in particular held some promise for survival benefit, based on early stage studies, but it did not ultimately demonstrate a significant increase in survival or pain relief. (Green 184:6-21, 202:13-23; PTX 452; PTX 455 at 1033; PTX 436 at 2403.)

Thus, despite the existence of 5-FU, the need for more effective chemotherapeutic agents for the treatment of solid tumors like those present in pancreatic cancer still existed in the early 1980s, at the time of the invention of gemcitabine and its anticancer utility. The use of gemcitabine to treat patients with advanced pancreatic cancer therefore satisfied this need and, although not a cure, became

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[23] To date, only eleven nucleoside drugs, including gemcitabine, have been approved by the FDA for the treatment of cancer. (Green 179 21-25.)

the accepted standard of care, which it remains today. (Green 178:23-179:11,204:25-205:17,205:18-23.)

Because of this effectiveness, gemcitabine, marketed as the commercial product Gemzar®, which embodies the inventions disclosed and claimed in the patents-in-suit, became and remains a commercial success.[24] Gemzar® is now Lilly's fourth-largest selling product worldwide, with net sales growing from $175 million in 1997 to $1.592 billion in 2007. (Grabowski Rep. ¶¶ 14, 35, Ex. 2.)[25] The evidence adduced at trial indicates that Lilly's marketing expenditures for Gemzar® equal about one-half of one percent of the net sales of Gemzar®, which is a marketing-to sales ratio lower than the average ratio for Gemzar®'s direct competitors as well as other relevant oncology drugs. (Id. at ¶¶ 18, 48-50, Ex. 6A-6B.)

Conclusions of Law

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[24] Defendants have conceded that their proposed product is a generic "copy" of Gemzar® that would infringe both the '614 patent and the '826 patent.

[25] Perhaps because of this commercial success, gemcitabine, the first nucleoside analog with a geminal difluoro substitution at the C-2' position, has engendered a relative boom in attempts to produce such nucleosides, with 40 having been reported in the literature by the year 2000. (PTX 620 at 87.) Of these, only gemcitabine has received FDA approval (Id. at 88.)

I. Standard of Review

Federal Circuit precedent governs matters of substantive patent law in this Court pursuant to 28 U.S.C. § 1295(a). Southwire Co. v. Essex Group, Inc., 220 U.S.P.Q. 1053, 1056 n.6 (N.D. Ill. 1983) ("The law that controls this action . . . is that law of the Federal Circuit[, which] has declared that the patent decisions of [the C.C.P.A.] will be considered binding . . . .") (citing S. Corp. v. United States, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (en banc)).

Patents are presumed to be valid. Moreover, each claim within a patent is independently presumed to be valid, even if other claims within that patent are held invalid. 35 U.S.C. § 282. Accordingly, the burden of proving invalidity rests with the patent challenger, here, Defendants, who must prove invalidity by clear and convincing evidence. Id.; Golden Blount, Inc. v. Robet H. Peterson Co., 365 F.3d 1054, 1061-62 (Fed. Cir. 2004). This burden "is constant and remains throughout the suit on the challenger" and "does not shift at any time to the patent owner." TP Labs., Inc. v. Prof'l Positioners, Inc., 724 F.2d 965, 971 (Fed. Cir. 1984). Pursuant to Defendants' obligation to carry this burden, "if the fact trier of the issue is left uncertain, the party with the burden loses." Tech Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008) (citation omitted).

If the patent challenger alleges invalidity based on prior art that was considered by the U.S. Patent and Trademark Office ("PTO") during the

prosecution of the patent, the challenger has the "added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000) (quoting Am. Hoist & Derrick Co. v. Sowa & Sons, 725 F.2d 1350, 1359 (Fed. Cir. 1984)); see also Impax Labs., Inc. v. Aventis Pharms. Inc., 468 F.3d 1366, 1378 (Fed. Cir. 2006) ("When the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity.") (citation omitted). The rationale underlying the presumption of validity is, however, "much diminished" when the prior art relied upon was not considered by the PTO during prosecution. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 426 (2007). That said, if a reference was not before the PTO examiner but was cumulative of others that were before the examiner, the heavy burden of proof nonetheless applies. Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1368 (Fed. Cir. 2004).

II. Effective Filing Dates of the Patents

Under 35 U.S.C. § 120:

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, . . . which is filed by an inventor or inventors named in the previously filed

> application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application. . . .

35 U.S.C. § 112, in turn, provides:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In accordance with these statutory provisions, the effective filing date of the '614 patent is March 10, 1983, the filing date of Dr. Hertel's original patent application containing a description of gemcitabine and a disclosure of a method of utility. (PTX 1.) The effective filing date of the '826 patent is December 4, 1984, the filing date of Dr. Hertel's and Dr. Grindey's original patent application

containing a description of a method of using gemcitabine to treat susceptible neoplasms. (PTX 2.)

III. Defendants' Claim of Double Patenting

In August 2009, summary judgment was entered against Lilly in the Eastern District of Michigan, in a factually similar case to the case before this Court, in which it was held that obviousness-type double patenting rendered the '826 patent invalid. Sun Pharm. Indus., Ltd. v. Eli Lilly & Co., 647 F.Supp.2d 820 (E.D. Mich. 2009). In handing down that ruling, the court addressed and resolved the exact same double patenting issue presented to us here. Defendants, accordingly, contend that Lilly is estopped from asserting in this litigation that the doctrine of obviousness-type double patenting does not apply.

Defendants invoke the rule promulgated by the Supreme Court in Blonder-Tongue v. University Foundation, 402 U.S. 313 (1971), which bars Plaintiff from relitigating the validity of the '826 patent. The Blonder-Tongue Court held that once a court determines that a patent is invalid in a proceeding where the patent owner had a full and fair opportunity to adjudicate the issue, the patent owner is collaterally estopped from relitigating the issue in a future case. Blonder-Tongue, 402 U.S. 313. Collateral estoppel limits patent owners to "one full and fair opportunity for judicial resolution of the same [invalidity] issue." Id. at 328. Blonder-Tongue also held that the application of collateral estoppel is

governed by "the trial courts' sense of justice and equity." Id. at 334.

Whether collateral estoppel applies is determined in accordance with Seventh Circuit precedent, rather than the Federal Circuit precedent which ordinarily controls in patent cases. Bayer AG. v. Biovail Corp., 279 F.3d 1340, 1345 (Fed. Cir. 2002). Thus, under Seventh Circuit precedent, for collateral estoppel to apply, "four elements must be met: '(1) the issue sought to be precluded must be the same as that involved in the prior litigation, (2) the issue must have been actually litigated, (3) the determination of the issue must have been essential to the final judgment, and (4) the party against whom estoppel is invoked must be fully represented in the prior action.'" Meyer v. Rigdon, 36 F.3d 1375, 1379 (7th Cir. 1994).

Further, "[c]laim preclusion (res judicata), as Rule 8(c) of the Federal Rules of Civil Procedure makes clear, is an affirmative defense," Rivet v. Regions Bank of Louisiana, 522 U.S. 470, 476 (1998), which "must be pleaded." Blonder-Tongue, 402 U.S. at 350. "The purpose of such pleading is to give the opposing party notice of the plea of estoppel and a chance to argue, if he can, why the imposition of estoppel would be inappropriate." Id.

We recognize that, in this case, Defendants did not plead collateral estoppel as an affirmative defense. However, it is equally clear that the likely reason for this deficiency is that the Eastern District of Michigan decision subjecting the issue of double

patenting as it relates to the '826 patent to collateral estoppel was handed down a mere month prior to the trial in the case at bar. Therefore, Defendants had no meaningful opportunity to plead it. Lilly contends that the pleading requirement is essential and must be upheld because Lilly was not given sufficient notice of the res judicata defense; however, Lilly's contention has been undermined by the fact that Lilly availed itself of an opportunity, in post-trial briefing of the issues before the Court, to argue at length why estoppel should not apply. Accordingly, rigid enforcement of the typical pleading requirement would serve only to undermine "justice and equity" in this case. Blonder-Tongue, 402 U.S. 334.

Upon review of the parties' arguments for and against the application of res judicata, we conclude that the four elements of collateral estoppel are clearly met here. Lilly implicitly concedes the first three elements of the collateral estoppel standard have been satisfied: (1) the double patenting issue presented is exactly the same; (2) the issue was actually litigated before the Sun Pharmaceutical Court; (3) final judgment was entered in Sun Pharmaceutical, based on the double-patenting issue. As to the fourth element, Lilly argues only that it was denied a full and fair opportunity to litigate the double patenting issue at trial because the Michigan court's summary judgment decision was "facially and indisputably wrong as a matter of law." (Pl.'s Tr. Br. at 36.) Although we do not here reject Lilly's arguments related to the merits of the Sun Pharmaceutical decision, we do hold that simply

disagreeing with the result at the summary judgment phase, which resulted in a final judgment for collateral estoppel purposes, see Smith v. City of Chicago, 820 F.2d 916 (7th Cir. 1987), is insufficient to demonstrate the lack of a full and fair representation in the prior litigation. Therefore, Lilly is estopped in this action from defending against Defendants' claim that the '826 patent is invalid for obviousness-type double patenting.[26]

IV. Anticipation[27]

A patent claim is invalid under 35 U.S.C. § 102(a) if "the invention was known or used by others in this country, or patented or described in a printed

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[26] The Court takes judicial notice of the fact that Lilly has appealed the judgment issued against it in Sun Pharm Indus., Ltd. v. Eli Lilly & Co., 647 F.Supp.2d 820 (E.D. Mich. 2009), and that the matter is currently pending before the Federal Circuit. We assume that the parties will return for reconsideration of our decision that collateral estoppel applies, should the Federal Circuit overturn Sun Pharmaceuticals. Although we make no prediction as to the outcome of that case on appeal, we note preliminarily that the trial record before this Court in our judgment largely supports Lilly's substantive contentions relating to obviousness-type double patenting.

[27] The decision in Sun Pharmaceutical did not address any of the remaining issues presented before this Court, including anticipation, obviousness, and enablement, as they relate to the '826 patent. Because the parties have maintained their dispute over these issues, and have not withdrawn their arguments in light of the Sun Pharmaceuticals decision, we address these issues fully on the complete trial record before the Court.

publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). Pursuant to 35 U.S.C. § 102, anticipation requires "the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim." Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 138 (Fed. Cir. 1986) (citation omitted).

Defendants, as challengers of the patents' validity, bear the burden of proving by clear and convincing evidence that the references relied upon to demonstrate anticipation are, in fact, prior art. Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1330 (Fed. Cir. 2004). To determine what constitutes prior art for invalidity analysis, the Court must consider the "invention date" for the asserted claim. 35 U.S.C. § 102(a); Muharkar v. C.R. Bard, Inc., 79 F.3d 1572, 1576 (Fed. Cir. 1996). Documents that are not prior art cannot anticipate a patent claim. IMX, Inc. v. Lendingtree, LLC, 2006 WL 47066, at *1 (D. Del. Jan. 10, 2006). In showing that all elements of an invention were anticipated, the challenging party may not rely upon the knowledge of one skilled in the art of the disclosure of another reference to supply missing elements. Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 715 (Fed. Cir. 1984).

A. Dr. Bobek's Slides

Defendants attempted at trial to show that a group of slides ("Bobek Slides") produced by Dr. Bobek anticipated the asserted claims of the '614

and '826 patents because those slides contained a drawing of the chemical structure of gemcitabine. (DTX 220 at Bobek 133.) We thus must first determine if these slides did in fact constitute prior art for invalidity purposes. Norian, 363 F.3d at 1330.

As a general matter, public presentations qualify as prior art under 35 U.S.C. §§ 102(a) and (b). See Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1369-70 (Fed. Cir. 2000); Mass Inst. of Tech. v. AB Fortia, 774 F.2d 1104, 1108 (Fed. Cir. 1985) (finding that a paper that was presented to persons in the relevant field qualified as a "printed publication" under § 102(b)). Defendants contend that Dr. Bobek's presentations were public, citing Dr. Bobek's testimony to that effect. (Bobek 1318:13-1319:25.) Aside from his testimony, however, no other evidence in the record supports Defendants' contention that these slides were ever disclosed or otherwise made known publicly. In fact, Dr. Rustum and Dr. Bernacki stated that they had no recollection of being present at any meeting where Dr. Bobek purportedly made a presentation disclosing his work on gem-difluoronucleosides, despite being Dr. Bobek's departmental colleagues during that period. (Rustum 1589:21-1590:2; Bernacki Dep. 51:16-23, 52:13-18.) Therefore, Dr. Bobek's testimony on this point is uncorroborated.

Defendants argue that his uncorroborated testimony is sufficient to establish that the public display of the presentation actually occurred, citing Thomson S.A. v. Quixote Corp., 166 F.3d 1172 (Fed.

Cir. 1999). The rule of Thomson - that the testimony of a "disinterested" witness need not be corroborated in certain circumstances - does not, however, apply to the present facts. Not only was Dr. Bobek a paid consultant of Defendants, but his testimony revealed his disappointment and resultant emotional reaction to his not having discovered and invented gemcitabine prior to Lilly's doing so. (Cf. Hertel 325:20-326:3; Farr Dep. 56:20-57:6.) Further, since deciding Thomson, the Federal Circuit has reiterated that "corroboration is required of any witness whose testimony alone is asserted to invalidate a patent, regardless of his or her level of interest." Finnigan corp. v. Int'l Trade Comm'n, 180 F.3d 1354, 1369 (Fed. Cir. 1999); see also Adenta GmbH v. Orthoarm, Inc., 501 F.3d 1364, 1371 (Fed. Cir. 2007). Accordingly, because the evidence in the record is insufficient to support a finding that the Bobek Slides were presented publicly in the form advanced by Defendants, we conclude that they do not qualify as prior art by virtue of their public presentation.

Assuming *arguendo* that Dr. Bobek's uncorroborated testimony established that the presentation was public and thus prior art, the Bobek Slides nonetheless constitute such limited a disclosure as to be entirely inadequate for a showing of anticipation. Regents of Univ. of Cal. v. Howmedica, Inc., 530 F. Supp. 846, 860 (D.N.J. 1981), affd, 676 F.2d 687 (3d Cir. 1982) ("[T]he projection of the slides at the lecture was limited in duration and could not disclose the invention to the extent necessary to enable a person of ordinary skill in the art to make or use the invention.").

Furthermore, Dr. Bobek's presentations were and are insufficient to anticipate the asserted claims because of their scant content. They do not contain any information about antitumor activity, nor are they capable of enabling a person of skill in the art to synthesize gemcitabine. "In order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation." Impax, 545 F.3d at 1314.

Defendants contend that Dr. Bobek invented gemcitabine prior to Lilly, but the record before the Court clearly shows that Dr. Bobek never, in fact, invented gemcitabine. Dr. Bobek admitted that he never isolated, characterized, or analyzed any product from the reaction that he asserts resulted in gemcitabine. (Bobek 1324:9-23, 1325:11-19, 1358:7-9, 1359:8-9; Radtke 459:12-463:3; PTX 499 at Bobek 202; PTX 508 at 61.) Moreover, Dr. Bobek never demonstrated any utility for gemcitabine, and therefore never actually reduced the compound he conceptualized in his slides to a practical invention. Dr. Bobek did not disclose his alleged invention of gemcitabine in a patent application, describe it in a published document, or use it publicly, and he eventually abandoned his work on the compound. For these reasons, Dr. Bobek's work cannot be treated as prior art; it cannot support Defendants' theory of prior invention; and it falls far short of anticipating the asserted claims. See Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1577 (Fed. Cir. 1996); Lutzket v. Plet, 843 F.2d 1364, 1366-67 (Fed. Cir. 1988).

Defendants also contend that Lilly was able to invent gemcitabine only because of information garnered from Dr. Bobek's work. They assert that Dr. Bobek communicated information relating to gemcitabine, in particular its capacity to function as an anticancer agent, to Dr. Grindey, a named inventor of the '826 patent, while both were employed at Roswell Park. A claim of derivation "requires a showing of both (1) prior conception of the invention by another and (2) communication of that conception to the patentee that is 'sufficient to enable [him] to construct and successfully operate the invention.'" Int'l Rectifier Corp. v. IXYS Corp., 361 F.3d 1363, 1376 (Fed. Cir. 2004).

For all of the reasons previously discussed, it is abundantly clear that Dr. Bobek did not conceive of gemcitabine and its utility prior to Lilly's having done so. "Conception requires both the idea of the invention's structure and possession of an operative method of making it." Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991). Although Dr. Bobek's slides contained a depiction of the structure of gemcitabine, he never devised a successful method for synthesizing the compound. Accordingly, Defendants have failed to prove by clear and convincing evidence that Lilly derived the invention of the '826 patent from Dr. Bobek's work.

Defendants also failed at trial to prove the "communication" required for a derivation claim. The only evidence Defendants offered to support this contention was Dr. Bobek's uncorroborated

testimony that he communicated his idea for using gemcitabine as an anticancer agent to Dr. Grindey. (Bobek 1311:11-1312:14.) In addition to being uncorroborated, Dr. Bobek's testimony is unconvincing because of its intrinsic inconsistency. At his deposition, Dr. Bobek alleged that Dr. Grindey had reviewed his 1975 grant proposal related to gemcitabine when Dr. Grindey acted as a grant reviewer for the American Cancer Society. (Bobek 1398:8-1399:5.)[28] By contrast, when the veracity of this assertion was challenged at trial, Dr. Bobek testified that Dr. Grindey reviewed the grant as an *in vivo* tester at Roswell Park. Given the inconsistencies inherent in this testimony and the evidence in the record clearly refuting Dr. Bobek's assertion that he communicated his ideas to Dr. Grindey, Defendants also cannot establish the second element of their derivation claim.

The derivation claim advanced by Defendants, which rests entirely on the uncorroborated testimony of Dr. Bobek, is reminiscent of an early observation by the Supreme Court:

> The very fact, which courts as well as the public have not failed to recognize, that almost every important patent. . . has been attacked by the testimony of

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[28] This averment is unconvincing because Dr. Grindey's curriculum vitae indicates that he was not on the American Cancer Society grant committee in 1975. (DTX 78 at GM 194054.)

> witnesses who imagined they had made similar discoveries long before the patentee had claimed to have invented his device, has tended to throw a certain amount of discredit upon all that class of evidence, and to demand that it be subjected to the closest scrutiny.

Barbed Wire Patent Case, 143 U.S. 275, 284-85 (1892). Dr. Bobek's testimony regarding his earlier conception of gemcitabine and its anticancer utility simply cannot withstand this sort of heightened scrutiny.

For all of these reasons, we hold that Defendants have failed to prove by clear and convincing evidence that Dr. Bobek's work anticipated that patents at issue in this suit.

B. Dr. Bergstrom's Work

1. The Bergstrom Abstract as Prior Art

Defendants also contend that the Bergstrom Abstract is prior art to the '614 patent under § 102(a) because it was published prior to March 10, 1983, the filing date of the first application in the chain that led to the patent. Defendants bear the burden of proving that this is prior art, Mahurkar, 79 F.3d at 1578, and "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the

reference." In re Stempel, 241 F.2d 755, 759 (C.C.P.A. 1957) see also In re Stryker, 435 F.2d 1340, 1341 (C.C.P.A. 1971).

In March 1983, the Bergstrom Abstract disclosed a 3',3'-difluoro-2',3'dideoxythymidine, a compound with the gem-difluoro substitution at the C-3' position and with a thymine base. This compound clearly was not gemcitabine. (PTX 518; Radtke 466:13-467:12.) By June 1982, Dr. Hertel had already described the structure of 2',2'-difluoro-2'-deoxynucleosides; devised a method for their synthesis; actually synthesized a 2',2'-gem-difluoronucleoside; and observed antiviral activity. (E.g., Hertel 311:17-313:4, 316:1-319:7, 330:8-24; PTX 26 at 162, 164; PTX 181; PTX 229.) Therefore, prior to the publication in March 1983 of the Bergstrom Abstract, Dr. Hertel had already invented more of the claimed invention than the Bergstrom Abstract disclosed. Accordingly, that abstract is not prior art and did not anticipate the '614 patent.

2. Failure to Disclose All Elements of the Invention

As discussed previously, the compound disclosed in the Bergstrom Abstract was a 3',3'-difluoro-2',3'-dideoxythymidine, a compound with the gem-difluoro substitution at the C-3' position and with a thymine base. Because this compound is not gemcitabine, the disclosure of the compound is insufficient to anticipate the invention of gemcitabine. Carella, 804 F.2d at 138. Moreover, the Bergstrom Abstract did not disclose the operable

method of making gemcitabine, which was another element of the claimed invention.

Nor is this a case in which the disclosure in the asserted prior art would cause one of ordinary skill to "at once envisage" the claimed compound. Bristol-Meyers Squibb v. Ben Venue Labs, Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001). Defendants contend that the Bergstrom Abstract discloses a small genus of compounds consisting of the natural bases coupled to 2' and 3' gem-difluorosugars, but the evidence clearly demonstrates that Dr. Bergstrom in no way limited his disclosure to the natural bases. (Radtke 471:5-15; Herdewijn 1098:23-1099:5; PTX 518.) Moreover, the evidence showed that Drs. Bobek, Bergstrom and Farr each considered making nucleoside analogs with non-natural bases. (E.g., PTX 533 at Bergstrom 20; PTX 494 at Bobek 18; PTX 498 at 68; Herdewijn 1090:7-16, 1091:5-18; PTX 555.) Thus, viewed in the proper context, the genus the abstract actually encompassed included a limitless number of molecules made with non-natural bases and therefore did not disclose gemcitabine to a person of ordinary skill in the art.

The Bergstrom Abstract at most disclosed the concept of making a similar compound. It did not constitute "the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim," Carella, 804 F.2d at 138, and therefore did not anticipate the asserted claims.

3. The Bergstrom Slides

Defendants also contend that slides numbered 3258 and 3261 of Dr. Bergstrom's March 1983 presentation at the Seattle American Chemical Society meeting ("Bergstrom Slides") anticipate both the '614 patent and the '826 patent. While they are correct that a public presentation such as this might qualify as prior art under 35 U.S.C. §§ 102(a) and (b), Ecolochem, 227 F.3d at 1369-70, the Bergstrom Slides to not qualify as prior art.

The Bergstrom Slides are not prior art to the '614 patent because the presentation occurred on March 23, 1983, *after* Dr. Hertel invented the claimed compounds and *after* Lilly filed the '883 application. (PTX 518; PTX 519.) In addition to not qualifying as prior art to the '614 patent, the slides do not contain sufficient information to enable one of ordinary skill in the art to make gemcitabine because they contain no synthetic routes capable of producing the compound, or its 2,2-difluororibose precursor. (Bergstrom 953:9-16.) Accordingly, the Bergstrom Slides do not anticipate claim 12 of the '614 patent. Amgen, 927 F.2d at 1206.

The Bergstrom Slides arguably do qualify as prior art to the '826 patent, given that they were published before the application leading to that patent. They cannot, however, be viewed to anticipate claim 7 of the '826 patent because the slides contain no information whatsoever about antitumor activity, which is essential to the claimed invention. Carella, 804 F.2d at 138. Finally, and more broadly, Defendants have failed to carry their

burden of proving anticipation by clear and convincing evidence, given that Dr. Bergstrom testified that he could not recall which slides he actually showed at the presentation, whether he discussed 2',2'-difluoronucleosides at the presentation, or whether he, in fact, proposed any utility for the compounds he did discuss during the presentation. (Bergstrom 952:15-18. 953:5-8, 917:24-918:6.)

C. The Merrell Dow Research

Defendants further contend that both claim 12 of the '614 patent and claim 7 of the '826 patent are anticipated by the alleged prior invention of those claims by Drs. Farr and Metcalf of Merrell Dow. In patent law, "priority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive the invention and that it exercised reasonable diligence in later reducing that invention to practice." Z4 Techs, Inc. v. Microsoft Corp., 507 F.3d 1340, 1352 (Fed. Cir. 2007) (citation omitted).

As an initial matter, the facts clearly demonstrate that Lilly reduced the invention to practice prior to any other party, including the researchers at Merrell Dow. Moreover, by the time Drs. Farr and Metcalf actually synthesized and tested gemcitabine, Lilly had already screened it for cytotoxity and administered it in a wide variety of tests. Indeed, Lilly had filed a patent application disclosing methods of treating cancer using gemcitabine. (PTX 118 at GM 157170; Hertel 334:1-

21; PTX 552; PTX 555) Therefore, in order to prove anticipation, Defendants must show that these Merrell Dow researchers first conceived of the claimed inventions and thereafter exercised reasonable diligence in reducing those inventions to practice.

1. The'614 Patent

Defendants concede that Merrell Dow did not actually produce gemcitabine before Lilly did, but contend nonetheless that Dr. Metcalf was the first to conceive of the compound, and Dr. Farr later worked diligently to reduce it to practice. Thus, we first address whether Dr. Metcalf conceived of gemcitabine prior to 1983. "Conception requires both the idea of the invention's structure and possession of an operative method of making it." Amgen, 927 F.2d at 1206. The evidence at trial did not establish that either Dr. Farr or Dr. Metcalf knew how to make gemcitabine at any time prior to Lilly. (PTX 554 at SA 2200; PTX 557 at SA 2182; PTX 566; PTX 6.)[29] In fact, when Merrell Dow eventually filed a patent application on difluoronucleosides, it disclosed Lilly's synthetic route, which had been previously described in Lilly's

[29] Further, Defendants' argument regarding the timing of Dr. Metcalf's alleged conception rests solely on his uncorroborated deposition testimony, which is insufficient as a matter of law. Finnigan Corp. v. Int'l Trade Comm'n, 180 F.3d 1354, 1369 (Fed. Cir. 1999).

published British patent application. (PTX 568, 17:47-51, 18:49-30:29; PTX 16, 4:43-9:47.)[30]

Thus, Defendants cannot show that the Merrell Dow researchers actually conceived of the claimed invention prior to Lilly, and their claim of anticipation or prior invention with regard to the '614 patent fails.

2. The '826 Patent

Defendants also contend that Merrell Dow has priority of invention with regard to the use of gemcitabine as an anticancer agent in mammals. Once again, in the face of clear evidence demonstrating that Lilly first reduced that utility to practice, Defendants argue that the Merrell Dow researchers conceived of the anticancer utility prior to Lilly and that therefore claim 7 of the '826 patent is invalid for anticipation under 35 U.S.C. § 102(g). The only thing Defendants have successfully proved by clear and convincing evidence, however, was that, *after* March 1984, Merrell Dow conceived of an anticancer utility for gemcitabine. As a review of the record shows, this is not proof that Merrell Dow was

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[30] We note that, while the original text of the '614 patent is available for assessing obviousness under 35 U.S.C § 103 as of its March 1983 effective filing date, it is not evidence of what was generally known in the art as of that date and may not be used as of that date to supplement what are otherwise inadequate disclosures or priority proofs of others In re Glass, 492 F.2d 1228, 1231-32 (C.C.P.A 1974).

the first to conceive of the anticancer utility or specifically that their discovery preceded Lilly's.

Prior to March 31, 1984, the Merrell Dow documents merely discussed a potential "antiviral activity" for different difluoronucleosides, not a confirmed anticancer activity for gemcitabine. (PTX 552 at SA 2206-07; PTX 553 at SA 2196-97.) By this point in time, Lilly had not only conceived of a potential anticancer utility for gemcitabine, but had tested the compound for such activity *in vitro* and *in vivo*. Dr. Hertel sent a sample of gemcitabine to Dr. Grindey for *in vitro* testing on October 11, 1983, and the sample was tested numerous times in November and December of 1983. (PTX 31 at 195; Hertel 332:25-335:4, 335:13-337:8; PTX 118 at GM 157170-76.) Dr. Grindey commenced *in vivo* anticancer testing in February 1984. (Pearce 90:16-91:9; PTX 126.)[31]

Accordingly, Defendants have failed to prove by clear and convincing evidence that the researchers at Merrell Dow conceived of the anticancer utility prior to Lilly, or worked to reduce that purported conception to practice. Therefore, the

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[31] Moreover, Defendants' reliance upon Dr. Metcalf as the prior conceiver of the anticancer utility is undercut and contradicted by the fact that, when Merrell Dow did finally file a patent application on their difluoronucleoside anticancer work, the patent application did not list Dr. Metcalf as an inventor. (PTX 568; DTX 895 at SA 1448.)

Merrell Dow work did not anticipate claim 7 of the '826 patent.[32]

For all of the foregoing reasons, Defendants have failed to establish that the patents-in-suit were anticipated, either by "the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim," Carella, 804 F.2d at 138, or under any alternative theory. Therefore, Defendants' claims of anticipation are unavailing.

V. Obviousness

Defendants also contend that both the '614 patent and the '826 patent are invalid for obviousness. Under the United States Patent Act, a patent cannot be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). A party seeking to invalidate a patent based on obviousness must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings and prior art references to achieve the claimed invention, and that the skilled

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[32] Just as Defendants clearly failed to show at trial that Lilly derived the invention of gemcitabine from Dr. Bobek, they also failed to show that Dr. Bobek's purported disclosure of gemcitabine anticipated Lilly's invention of the compound. See supra § IV A.

artisan would have had a reasonable expectation of success in doing so." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) (citations omitted).

"[T]he outcome of the trial on this point will depend on whether, in light of all the evidence, the party challenging the patent's validity has carried its burden to prove by clear and convincing evidence that the patent is invalid." Titan Tire Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1376 (Fed. Cir. 2009). Moreover, where, as here, the patent challenger alleges invalidity based on prior art that the Patent and Trademark Office ("PTO") considered during prosecution of the patent or cumulative with art considered by the PTO, the challenger has the "[a]dded burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." Ultra-Tex Surfaces, 204 F.3d at 1367.

Obviousness is a question of law based on underlying findings of fact, which include: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. Proctor & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (citing Graham v. John Deere Co., 383 U.S. 1, 17 (1966)). "[I]ncluded within the [patent's] presumption of validity is . . . a presumption of nonobviousness." Structural Rubber Prods., 749 F.2d at 715.

Obviousness arises when a skilled individual "merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" In re Kubin, 561 F.3d 1352, 1359 (Fed. Cir. 2009) (quoting KSR Int'l., 550 U.S. 398, 421 (2007)). Section 103 also bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." KSR Int'l, 550 U.S. at 417. Obviousness does not require absolute predictability; all that is required is a reasonable expectation of success. Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006) (citing In re Longi, 759 F.2d 887, 896 (Fed. Cir. 1985)).

The reference or evidence used to establish obviousness under 35 U.S.C. § 103 must qualify as prior art under one or more sections of 35 U.S.C. § 102. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1568 (Fed. Cir. 1987). What a reference teaches is a question of fact addressed to a hypothetical "person of ordinary skill in the art." In re Bell, 991 F.2d 781, 783-84 (Fed. Cir. 1993). To prove that a claimed invention was obvious, a patent challenger must demonstrate "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007).

A. The '614 Patent

1. No Prior Invention

Defendants contend that, prior to the filing of the applications leading to the '614 patent and '826 patent, three different research endeavors - those of Drs. Bobek, Bergstrom, and Metcalf and Farr - proposed gemcitabine and its use as an antiviral or antitumor agent. A finding of contemporaneous or prior invention "can be understood to suggest that one of ordinary skill in the art would have been motivated to combine prior art references to arrive at the claimed invention," and that therefore the invention would have been obvious. Nat'l Steel Co., Ltd. v. Canadian Pac. Rv., Ltd., 357 F.3d 1319, 1337-38 (Fed. Cir. 2004).

Defendants' reliance upon the work done by these researchers is, however, misplaced because those scientists' attempts to make gemcitabine were both partial and ultimately unsuccessful. The failures of contemporaneous or prior research to create the claimed invention can be determinative of nonobviousness. Advanced Display Sys. Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000); Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1088 (Fed. Cir. 2008); Forest Labs., Inc. v. Ivax Pharms, Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007).

Indeed, the evidence at trial relating to the efforts of these researchers clearly shows that a person of ordinary skill in the art would not have known how to make gemcitabine. Collectively, Drs. Bergstrom, Bobek, and Farr spent numerous years pursuing various synthetic methods in attempting to

make geminally substituted difluoronucleoside analogs. These synthetic approaches included: (1) direct fluorination of a nucleoside; (2) direct fluorination of a sugar followed by coupling to a base; (3) direct fluorination of a six-membered ring sugar, followed by conversion to a five-membered ring sugar, followed by coupling to a base; (4) *de novo* synthesis involving a Sharpless epoxidation step; and (5) *de novo* synthesis using D-glyceraldehyde acetonide as a starting material. (E.g., Radtke 496:5-497:4, 498:9-499:2; Bergstrom 905:22-906:2, 911:9-18, 945:6-24; Bobek 1359:5-9; Overman 613:13-621:9; PTX 498 at Bobek 66-68; PTX 494 at Bobek 17-18; PTX 535 at 265; Dep. of Farr 117:13-17.) In light of the fact that all of these methods were attempted and unsuccessfully so in the years leading up to and including the time that Lilly invented gemcitabine, it is abundantly clear that a person of ordinary skill in the art would have been uncertain as to how to synthesize gemcitabine.[33]

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[33] For a compound to have been obvious, a person of skill in the art must have been able to synthesize that compound without undue experimentation. Accordingly, naming or sketching that compound is insufficient. See In re Brown, 329 F.2d 1006, 1010-11 (C.C.P.A. 1964); In re Wiggins, 488 F.2d 538, 543 (C.C.P.A. 1973); In re Samour, 571 F.2d 559, 563 (C.C.P.A. 1978). Therefore, although proposed sketches of gemcitabine were contained in contemporaneous research, the experimental failures of all researchers outside of Lilly demonstrate the nonobviousness of the asserted claims.

2. Defendants' Attempts to Rationalize Experimental Failures

Through expert testimony, Defendants unconvincingly attempt to discount the failures of Drs. Bobek, Bergstrom, Metcalf, and Farr to create gemcitabine. First, Defendants seek to divert attention from the difficulty of synthesizing gemcitabine by highlighting expert testimony that Dr. Hertel's synthetic route would have been the obvious choice for the person of ordinary skill in the art. Dr. Herdewijn averred that a person of ordinary skill would not have attempted direct fluorination of a nucleoside, (Herdewijn 1028:15-22), and Dr. Kathlyn Parker stated that "only" Dr. Hertel's synthetic route would have been pursued by the person of ordinary skill in the art. (Parker 1169:5-1170:9, 1193:24-1194:9). These opinions ignore the alternate synthetic routes employed by other researchers, however, and are directly contradicted by the facts of the case. For example, the evidence clearly demonstrated that Dr. Bergstrom did himself, in fact, attempt direct fluorination of a nucleoside. (Bergstrom 946:23-948:5; Radtke 509:9-23; PTX-534 at Bergstrom 67, 69.)[34]

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[34] Casting further doubt on Dr Herdewijn's opinion regarding the synthesis methods is the fact that he contended that DAST could be used to make the C-2 difluorinated sugar precursor of gemcitabine, (Herdewijn 1032:16-22), ignoring a clear admission to the contrary by Dr. Bergstrom: "Attempts at direct fluorination of 2-ketofuranose derivatives using DAST to afford the corresponding 2,2-difluoro derivatives have not been successful." (PTX 535 at 362.) Indeed, Dr Herdewijn acknowledged, in a separate portion of his testimony, that the

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It is equally clear that some of the expert testimony Defendants rely upon was arrived at inappropriately. Dr. Parker admitted that she was aware of Dr. Hertel's successful approach before she conducted her expert analysis; that she never considered the work of Drs. Bobek, Bergstrom, and Farr; that she did not consider any Lilly work other than the successful synthesis reported in the '614 patent; and that she limited her review of the prior art to those references that supported "the story that [she] was telling." (Parker 1168:18-22, 1170:14-23, 1171:15-21, 1178:19-23, 1179:23-1180:18, 1182:16-18). As the Federal Circuit has held, such hindsight-driven analysis cannot be used to refute clear evidence to the contrary. Ortho-McNeil Pharm., Inc. v. Mylan Labs., 520 F.3d at 1364 ("[The] expert . . . simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention . . . was obvious. Of course, this reasoning is always inappropriate . . . .").

Fact finders must avoid "[t]he distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." KSR

(...continued)

DAST approach failed when attempted at other positions on the sugar, and he offered no explanation as to why the C-2 position would be different. (Herdewijn 1058:10-14, 1059:15-1060:10.) "[T]here must be some factual support for an expert's conclusory opinion." Upjohn Co. v. Mova Pharm. Corp., 225 F.3d 1306, 1311 (Fed. Cir. 2000).

Int'l, 550 U.S. at 421 (citing Graham, 383 U.S. at 36). In light of this guidance, we find that the more appropriate conclusion was the one drawn by Dr. Overman, who after reviewing all of the attempts by other researchers to create gemcitabine alongside Dr. Hertel's work, concluded that at least five categories of synthetic routes were available to a person of ordinary skill in the art and that such a person would not have known which route held the most promise for the successful synthesis of gemcitabine. (Overman 596:7-597:6, 603:2-605:10, 606:20-607:11, 608:13-23, 649:16-49, 650:21-24, 698:8-13, 711:13-16; LDX 9.4; LDX 9.22.)

Dr. Herdewijn also attempted to explain away the failures of Drs. Farr and Bergstrom by referencing the fact that they utilized the expertise of a general organic chemist, rather than the specialized expertise of a nucleoside chemist. (Herdewijn 983:14-25, 1047:12-19, 1052:22-1053:2.) However, Dr. Herdewijn's explanation of the significance of this expertise is unavailing, given the fact that Dr. Bobek, himself a nucleoside chemist, also repeatedly failed to synthesize gemcitabine using the same methodology. Further, the vast majority of the experimentation failures experienced by Drs. Farr and Bergstrom occurred during steps in the synthetic process that did not require nucleoside chemistry expertise. (Herdewijn 984:6-14 (identifying only one reaction that allegedly involved expertise specific to a nucleoside chemist).)[35]

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[35] Moreover, Defendants' contention that only a nucleoside chemist had the skill to make gemcitabine is (continued...)

Finally, Dr. Herdewijn attempted to rationalize Dr. Farr's failures by testifying that Dr. Farr would have succeeded had he been in possession of an article authored by Poulter and colleagues. (PTX 797). Dr. Herdewijn's opinion in this regard is again unfounded, however, because Dr. Farr was independently aware of the important information contained in that article during the period when he was attempting to synthesize gemcitabine and yet he still failed to make the compound. (PTX 552 at SA 2212-13; PTX 553 at SA 2200; Overman 630:20-631:21.) Accordingly, because Dr. Farr was in possession of this information, the alleged absence of access to the Poulter article cannot rationalize, explain, or supersede, his failure to create gemcitabine.

In the end, Defendants' experts fail in their attempts to explain away the failures of Drs. Bobek, Bergstrom, and Farr. Thus, all that is left in the evidence is the clear fact of those failures. Neither Dr. Parker nor Dr. Herdewijn testified that Dr. Bobek actually synthesized gemcitabine, and the facts adduced clearly show that the route he

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directly contradicted by the facts. Drs. Bobek and Bergstrom, both nucleoside chemists, failed to make the compound, whereas Dr. Hertel, who had a background other than that in nucleoside chemistry, was the first to succeed in synthesizing gemcitabine. (Hertel 353-13-15 ("[W]hat I brought to the table, not having a background in nucleoside chemistry, was that I didn't have blinders on how you need to make nucleosides.").)

proposed was incapable of producing such a successful synthesis. (E.g., Radtke 459:12-461:8; Bobek 1358:8-9); PTX 492 at 3435; PTX 494 at Bobek 17.) Additionally, Dr. Bergstrom's failure, in which he utilized several different synthetic routes to create gemcitabine, is also well documented in the record. (Bergstrom 920:18-20, 946:23948:5; PTX 534 at Bergstrom 67-69; Radtke 509:9-23.) And contemporaneous to the invention of the '614 patent, the evidence reveals that Dr. Farr had only attempted a combination synthesis using Sharpless epoxidation, which also failed to create gemcitabine. (PTX 552 at SA 2212-13; PTX 553 at SA 2200; Overman 630:20-631:21.)

Accordingly, Defendants have failed to carry their burden to establish that a person of ordinary skill in the art could have used any of the methods other than that used by Dr. Hertel to synthesize gemcitabine, and have likewise failed to show that his method would have been known or obvious to, or anticipated by, a person of ordinary skill in the art. Titan Tire Corp., 566 F.3d at 1367-77. As these researchers' repeated unsuccessful attempts to synthesize gemcitabine demonstrate, the person of ordinary skill in the art did not and would not have known how to synthesize gemcitabine. Compare Advanced Display Sys, 212 F.3d at 1285 ("Zhou's deposition furnishes persuasive evidence that the West patent is nonobvious by describing ADS's repeated failures to design the claimed invention.'") to In re Merck & Co., 800 F.2d 1091, 1098 (Fed. Cir. 1986) (finding obviousness where four other groups independently and successfully invented the claimed

invention). Defendants, therefore, have not proved by clear and convincing evidence that the invention of the '614 patent would have been obvious. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

3. Obviousness Based on Structural Similarity

In challenging the validity of the '614 patent, Defendants also attempt to establish "obviousness based on structural similarity," which "may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound." Altana Pharm AG v. Teva Pharms. USA, Inc., 566 F.3d 999, 1007 (Fed. Cir. 2009). According to Defendants, one of ordinary skill in the art would have been motivated to create gemcitabine by the promising characteristics of three structurally similar compounds: *Ara*-C, 2'-F-*ara*-C, and 2'-F-cytidine.

Defendants assert that a "sufficiently close" relationship between gemcitabine and those three compounds would have "create[d] an expectation that" gemcitabine would have similar, perhaps improved antiviral and anticancer properties over those compounds. In re Dillon, 919 F.2d 688 (Fed. Cir. 1990). Defendants first contend that *Ara*-C, an FDA-approved drug used to treat patients with various leukemias, would have been a lead compound for the person of ordinary skill, and that the person of ordinary skill would have been motivated to modify *Ara*-C with a *gem*-difluoro

substitution at the 2'-position.[36] However, although *Ara*-C was "good as an anticancer drug" at the time of the development of gemcitabine, researchers were looking for alternatives to *Ara*-C that might exhibit improved anticancer activity. (Rustum 1545:10-1546:19; Radtke 542:15-19; PTX 693.) Included in those alternatives were 2'-F-*ara*-C and 2'-F-cytidine, which Defendants assert also had promising anticancer properties that would have motivated a person of ordinary skill to arrive at gemcitabine.[37]

Assessment of the obviousness of a chemical compound cannot be based merely on comparisons between that compound's chemical structure and structures in the prior art. In re Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963). There must be "some reason that would have led a chemist to modify a known compound in a particular manner" to establish obviousness by structural similarity. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

Upon review of the record of evidence adduced at trial, we conclude that Defendants' have failed to prove obviousness by virtue of gemcitabine's structural similarity to those three compounds because: (1) the prior art lacked any meaningful

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[36] Like gemcitabine, *Ara*-C is an analog of the naturally occurring nucleosides cytidine and deoxycytidine.

[37] These compounds differ from *ara*-C in only one respect: they each have a fluorine atom at the 2' position

precedent for gemcitabine; (2) the fluorination required to make gemcitabine was too unpredictable to create a reasonable, motivating expectation; and (3) the purported "promise" of compounds in the prior art was too insignificant to motivate one of ordinary skill in the art.

The prior art contained no clear indication that a difluorinated nucleoside analog would exhibit the activity demonstrated by gemcitabine. Indeed, no geminally substituted difluorinated nucleoside analogs existed in the prior art, and the biological activity of a geminal substitution at the C-2' position had never, in fact, been explored. (Radtke 435:15-25; 466:13-467:15, 470:13-25.) Moreover, because the monofluorinated nucleoside analogs that were contained in the prior art exhibited less *in vitro* cytotoxicity than *Ara*-C, which has no fluorine atoms, fluorination in general remained of questionable desirability. (E.g., PTX 587; Shewach 789:12-790:20)

Viewed more broadly, the record clearly indicates that a person of ordinary skill in the art would have known that the category of nucleoside analog into which gemcitabine falls is notoriously unpredictable. As the Federal Circuit has held, the suggestion that one chemical compound would have been obvious from a different but structurally similar compound generally rests on the assumption that small changes would not materially alter the properties of the parent compound. In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). However, where the evidence shows that small changes alter the

resulting properties significantly, that assumption is refuted, and a case for obviousness by structural similarity is greatly diminished. Papesch, 315 F.2d at 391.

At the time of Lilly's invention of gemcitabine, it was a common perception that fluorination often had drastic effects on the chemical properties of nucleoside analogs. (Radtke 434:5-435:2; Bergstrom 935:15-936:22.) Dr. Bobek wrote in a grant application prepared contemporaneous to Lilly's invention of the claims in the '614 patent that "it is very difficult to predict the biological behavior of e.g. 2',2'-gem-difluorocytidine." (PTX 498 at Bobek 69.) Dr. Bergstrom corroborated this view, testifying that one "can't predict" whether a CF_2 group would have the positive effect on biological activity that nucleoside researchers were hoping to attain. (Bergstrom 892:3-5.) Dr. Bergstrom further wrote that the activity of a nucleoside modified by fluorination "may be significantly different" and admitted that "the CF2 group may behave quite different in its effect on the structure and ultimately on biological activity." (PTX 533 at Bergstrom.) Additionally, Dr. Rustum acknowledged his surprise at the effectiveness of gemcitabine, given the unpredictable effects of fluorination. (Rustum 1617:9-18.)

Based on this evidence, it is clear that one of ordinary skill in the art at the time would have known that even minor changes in the structure of a nucleoside analog were capable of unpredictable effects on biological activity. (Radtke 434:5-435:14,

473:16-22; PTX-533 at Bergstrom 21.) Therefore, Defendants cannot prove obviousness simply by claiming that gemcitabine, by virtue of its structural similarity with other compounds, would have had reasonably expected properties. Soni, 54 F.3d at 750; see also Takeda Chem., 492 F.3d at 1356.

Finally, the record demonstrates that Defendants have overstated the promising antiviral and anticancer attributes offered - and thus the motivation engendered - by *Ara*-C, 2'-F-cytidine, and 2'-F-*ara*-C. Although *Ara*-C was "good as an anticancer drug," its usefulness was limited to leukemia, and not to the solid tumors that gemcitabine is used to treat. (Radtke 541:20-22.) Moreover, although *Ara*-C had demonstrated antiviral activity in some regard, this activity was never successfully shown in clinical tests, and a 1973 clinical study clearly discouraged the use of the compound as an antiviral agent. (PTX 473 at 1281.)

Defendants' contentions that 2'-F-cytidine and 2'-F-*ara*-C were promising compounds is similarly misplaced. Prior to the invention dates of the asserted claims, 2'-F-*ara*-C and 2'-F-cytidine had been reported in the prior art literature. Dr. Rustum testified that 2'-F-cytidine was reported to have properties that could lead to improved antitumor activity over *Ara*-C. (Rustum 1533:21-1534:3.) However, both compounds were significantly less cytotoxic *in vitro* than *Ara*-C. (Shewach 789:12-790:4; Radtke 445:5-446:11; PTX-583 at 205; PTX-587 at 23.) Furthermore, neither compound showed promising antiviral activity, and

neither was reported in the prior art to have been tested *in vivo*. (Shewach 752:25-753:10; Radtke 440:25-441:6, 451:1-452:8.) Because of such deficiencies, these compounds were bypassed in favor of other compounds in research conducted in the years prior to the filing of the patents in suit. (Radtke 44:25-441:6, 454:24-455:6.) Therefore, any motivation engendered by those compounds was, at best, minimal.

"Patents are not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." Procter & Gamble Co. v. Teva Pharms. USA. Inc., 566 F.3d 989, 997 (Fed. Cir. 2009) (quotation omitted). Dr. Hertel was clearly following the "general guidance" of the field. Defendants have adduced no evidence, however, that he was motivated by those three structurally similar compounds to create gemcitabine, nor does the evidence adduced support a finding that one of ordinary skill would have been so motivated.

For all of these reasons, Defendants have failed to establish "obviousness by structural similarity" with regard to the '614 patent.

B. The '826 Patent

Defendants also contend that the invention of the '826 patent would have been obvious based on

gemcitabine's structure and known antiviral properties, as well as its similarity to *Ara*-C, 2'-F-*ara*-C, and 2'-F-cytidine. They stress that, whereas obviousness in the context of the '614 patent depended upon the motivation to *create* gemcitabine, the question of obviousness as it relates to the '826 patent focuses on whether the person of ordinary skill in the art would have been motivated to use gemcitabine, which had already been invented, as an anticancer agent.[38]

1. The Difficulty of Discovering Antitumor Activity

As an initial matter, it is important to note the context of Defendants' obviousness contention, i.e., the particularly challenging field of designing and discovering anticancer drugs. As Dr. Rustum acknowledged, such drug design is "a very difficult process."[39] This is illustrated by the experience of

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[38] Because the "effective filing date" of the '614 patent is March 1983, its use as prior art for the '826 patent, although acceptable under 35 U.S.C § 102, is limited to the original application text, which does not include the later-discovered reference to the anticancer activity of gemcitabine. In re Lund, 376 F.2d 982, 988 (C.C.P.A. 1967); (see also Rustum 1610.15-18.)

[39] While Dr. Rustum asserted that one of ordinary skill in the art would have reasonably expected gemcitabine to be successful, he supported this theory by asserting (unconvincingly) that every molecule that Dr. Bobek made at Roswell Park, as well as every molecule made by many other chemists, was created and tested with a "reasonable expectation" of success based on what

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researchers at Roswell Park, which has never advanced a new chemical beyond early phase testing in an anticancer trial. (Rustum 1576:2-1578:11; see also Bobek 1414:24-1415:12.) Indeed, a 1979 article indicated that the "diligence of numerous investigators in cancer research as well as the difficulty of the problem are attested to by the fact that out of the nearly 300,000 compounds that have been evaluated as anticancer agents 40 or so are today considered useful . . . ." (PTX 692 at 3; Shewach 744:8-745:8.) This background is critical to an understanding of what the "reasonable expectations" of a person of ordinary skill in the art would have been in relation to gemcitabine's potential anticancer utility.

Defendants' obviousness claim relating to the '826 patent is divided into two parts: First, Defendants argue that the antiviral properties reported for *Ara*-C and 2'-F-*ara*-C would have led a person of ordinary skill to expect anticancer activity in gemcitabine, which had previously shown antiviral activity. Second, they contend that the prior art data on 2'-F-*ara*-C and 2'-F-cytidine pointed directly toward gemcitabine's potential for antitumor activity.

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was known from the prior art (Rustum 1577:19-1578:7.) This claim is contrary to the other, more convincing evidence adduced at trial

2. The Relationship Between Antiviral and Antitumor Activity

Defendants first contend that the antitumor activity of gemcitabine would have been obvious in light of its known antiviral activity. (Rustum 1536:14-19.) However, the prior art taught that antitumor activity could not necessarily be predicted from antiviral activity. (E.g., Shewach 749:18-750:14; PTX 721 at 567.) As the Fox Group at Sloan-Kettering discovered, often high antiviral activity correlated with low cytotoxicity. (Shewach 751:14-752:111; PTX 587 at 22.)

At certain points, Defendants concede that a general "inverse relationship" exists between antiviral activity and cytotoxicity. Relying on the Watanabe reference,[40] however, they contend that this relationship did not apply with regard to 2'-F-*ara*-C, which Watanabe reported to have both antiviral and anticancer activity (in other words, a "direct relationship" between the two). According to Defendants, a person of ordinary skill in the art would have read Watanabe as creating a motivating expectation that a "direct relationship" between antiviral and anticancer activity would be present in gemcitabine because of that compound's similarity to 2'-F-cytidine.

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[40] Kyoichi Watanabe et al, Nucleosides. 110 Synthesis and Antiherpes Virus Activity of Some 2'-Fluoro-2'-deoxyarabinofuransylpyrimidine Nucleosides, 22 J Med Chem 21, 21-24 (1977) (DTX 250).

Defendants far overstate the significance of this Watanabe data. Considering the entirety of the reference in the proper context, it is clear that Watanabe's findings would not have actually *motivated* a person of ordinary skill to develop gemcitabine for anticancer activity because 2'-F-*ara*-C was not the most promising antitumor agent of the compounds tested in that study. (PTX 587 at 22.) In fact, the prior art, including Watanabe and other studies, contained no significant data for 2'-F-cytidine's anticancer activity. Not only does the prior art not report any *in vivo* activity for 2'-F-*ara*-C, (Radtke 453:3-10, 454:13-18; Shewach 752:25-753:10; Herdewijn 1067:17-22.), but also Table II of Watanabe reported that this analog was two and one-half times less cytotoxic than *Ara*-C.

Indeed, the text of Watanabe does not suggest that 2'-F-*ara*-C was the most promising compound for any purpose. Watanabe instead selected FIAC and FMAU as the most "potent and selective" compounds and proposed them for *in vivo* testing. (PTX 584 at 27, 30, 36, 38; Radtke 454:19-455:6.) Defendants have not adduced any evidence suggesting why a person of ordinary skill would have diregarded the textual teaching of Watanabe and the mediocre cytotoxicity data for 2'-F-*ara*-C contained therein.[41] Defendants' reliance on Watanabe is

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[41] Furthermore, although the Watanabe reference was not before the PTO during prosecution of the '826 patent, (see DTX 2), the '773 patent was considered by the PTO which contained a comparable disclosure (DTX 223.) Ultra-Tex Surfaces, 204 F.3d at 1367.

clearly an attempt to reconstruct the data available to the person of ordinary skill in the art at the time with the benefit of hindsight, which is inappropriate. Interconnect Planning, 774 F.2d at 1143.

Because no evidence suggests that a person of ordinary skill in the art would actually have had a reasonable expectation of gemcitabine's antitumor properties based on Watanabe or other prior art in 1984, Defendants have failed to establish the obviousness of gemcitabine's antitumor activity based on its established antiviral activity.

3. The Cytotoxicity of 2'-F-*ara*-C and 2'-F-cytidine

Defendants also attempt to prove that 2'-F-*ara*-C and 2'-F-cytidine had antitumor activity, including the capacity to inhibit RNR and the potential for decreased deamination, that would have motivated the person of ordinary skill in the art to use gemcitabine as an antitumor agent.

The Stubbe paper[42] taught that 2'-F-cytidine was an RNR inhibitor, giving it potentially improved antitumor activity over *Ara*-C. (DTX 252; Rustum 1535:16-20.) Thus, according to Defendants, because, like 2'-F-cytidine, gemcitabine has a

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[42] J. Stubbe & J.W. Kozarich, Fluoride Pyrophosphate, and Base Release from 2'-Deoxy-2'-fluoronucleoside 5'-Diphosphates by Ribonucleoside-Diphosphate Reductase, 255 J. Biol Chem 5511, 5511-13 (1980) (DTX 252).

fluorine atom in the 2'-down position, a person of ordinary skill in the art would have been motivated to use gemcitabine to inhibit RNR. (Rustum 1546:5-19; Herdewijn 1023:20-1024:4.)

In advancing this argument, however, Defendants mischaracterize the results reported in the Stubbe paper. Dr. Stubbe reported that another compound, 2'-deoxy-2'-fluoroadenosine, was fifty times more effective as an inhibitor than 2'-F-cytidine. (Shewach 782:9-783:1; PTX 611 at 5511.) Furthermore, Defendants ignore another prominent study, the Brox paper,[43] which provided evidence against 2'-F-cytidine's capacity to inhibit RNR to a significant degree. (Shewach 792:3-15; PTX 593 at 1841; LDX 8.38.) Indeed, when Dr. Bergstrom later created a slide entitled "Biologically Significant Fluronucleosides," he included FIAC and 2'-deoxy-2'-fluoroadenosine, but he made no mention of 2'-F-cytidine or 2'-F-*ara*-C. (PTX 541 at 3257; Herdewijn 1118:24-1119:11.)

Therefore, a person of ordinary skill in the art would not have concluded, based on the Stubbe paper, that 2'-F-cytidine was an especially potent inhibitor of RNR.[44] Rather, a person of ordinary

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[43] L.W. Brox et al, Studies on the Growth Inhibition and Metabolism of 2'-Deoxy-2'-fluorocytidine in Cultured Human Lymphoblasts, 34 Cancer Res. 1838, 1838-42 (DTX 241).

[44] Notably, 2'-F-cytidine and gemcitabine inhibit RNR by way of completely different mechanisms, a fact that confirms the

(continued...)

skill would have drawn a conclusion similar to the one drawn by Dr. Bergstrom, who expressed a motivation to develop 2'-deoxy-2'-fluoroadenosine 5'-diphosphate, the molecule clearly emphasized in the Stubbe paper. (PTX 534 at Bergstrom 60; PTX 541 at Bergstrom 3257; Bergstrom 901:19-22, 940:25-941:18; Herdewijn 1118:24-1119:11; PTX 611.)

Aside from the Stubbe reference, the record at trial clearly shows that researchers at the time were not motivated by 2'-F-cytidine to propose difluoronucleoside analogs like gemcitabine as anticancer agents. For example, the researchers at Merrell Dow as well as Dr. Bergstrom never expressed any expectation that 2',2'-difluronucleosides would inhibit RNR, only that they "hoped" this activity, among a list of many possible activities, would be present. (Metcalf Dep. 34:11-12; Farr Dep. 27:6-13; PTX 534 at Bergstrom 47.) [45] Defendants have, at most, successfully demonstrated by clear and convincing evidence that a person of ordinary skill would have been uncertain as to what to expect of a compound like gemcitabine based on

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(...continued)
lack of a reasonable expectation of a relationship between the two compounds. (Shewach 783:16-787:6.)

[45] That this rose only to the level of a "hope" may have been because the only evidence suggesting the possibility that 2',2'-difluoronucleosides would exhibit antitumor activity arose out of *in vitro* testing of cytotoxicity, which is not indicative of the more important goal, *in vivo* demonstration of anticancer activity. (Rustum 1586:13-15; Shewach 795:23-797:7.)

the results in the prior art. The record contains no clear prior or contemporaneous teaching toward the use of gemcitabine to treat tumors.

Finally, the unpredictability of difluoronucleoside chemistry further undermines Defendants' obviousness claim. As the prior art taught, the presence of two fluorine atoms on the same carbon atom materially alters the structure and therefore the biological activity of the molecule. (Bergstrom 936:24-937:11; PTX-533 at Bergstrom 21.) Thus, even assuming *arguendo* that 2'-F-*ara*-C or 2'-F-cytidine showed the promise urged by Defendants, the biological effects produced by these monofluorinated molecules would not have provided a reasonable example of what to expect in a difluorinated molecule like gemcitabine. (Bergstrom 935:15-936:22.)[46]

For the foregoing reasons, Defendants have failed to demonstrate that either the antiviral activity or the anticancer activity of compounds contained the prior art would have created a

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[46] Further, Defendants admit that nothing in the original application leading to the '614 patent "singled out" gemcitabine from the other nucleoside analogs that were disclosed (Lee 1652.4-8, Hertel 383:13-384 2, 385:25-386 15; PTX-6). An invention would not have been obvious if one of ordinary skill could only "try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior at [gives] . . . no direction as to which of many possible choices is likely to be successful." Procter & Gamble Co v Teva Pharms. USA Inc., 566 F 3d 989, 996-97 (Fed. Cir. 2009).

reasonable, motivating expectation of such activity in gemcitabine. Therefore, Defendants' claim of obviousness based on this theory fails.

C. Objective Evidence of Nonobviousness

A court is obligated to consider objective evidence of nonobviousness when such evidence is present. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 960 (Fed. Cir. 1986); Knoll Pharm. Co. v. Teva Pharms. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004). In the case at bar, Lilly has demonstrated a nexus between the claimed inventions and various secondary considerations, which we therefore consider. Brown & Williamson Tobacco Cop, v. Philip Morris, 229 F.3d 1120, 1130 (Fed. Cir. 2000).[47]

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[47] "Defendants contend that Lilly cannot rely upon secondary considerations to show nonobviousness for the '826 patent because the '614 patent gave Lilly a monopoly on all uses of gemcitabine. This misstates the purpose of requiring the disclosure of a patented invention, which is to give the public an opportunity to learn from and improve upon it. This is why the patent statute expressly provides for patents on new uses of old compositions, as well as the "domination" of subsequent improvement patents by earlier basic patents. See 35 U.S.C. §§ 101; 100(b). In re Kaplan, 789 F.2d 1574, 1577-78 (Fed. Cir. 1986). The patentability of such improvement inventions is established by objective evidence of nonobviousness, notwithstanding the "domination" of an earlier patent. Eli Lilly & Co. v. Zenith Goldline Pharms. Inc., 471 F.3d 1369, 1379 (Fed. Cir. 2006). Further, Defendants' contention that the '614 patent "blocked" the development of gemcitabine as anticancer agent is unsupported, the case Defendants cite in support, Merck & Co. v.

(continued...)

1. Gemcitabine's Unexpected Properties

An invention's unexpected positive properties support the conclusion that the invention would not have been obvious. Procter & Gamble, 566 F.3d at 997. Gemcitabine showed numerous capabilities that were not hinted at in the prior art, including: (1) superior accumulation and retention in cancer cells; (2) enhanced interference with DNA synthesis; and (3) enhanced inhibition of RNR. (Shewach 754:4-764:8, 785:1-786:10.) Furthermore, gemcitabine was particularly effective against solid tumors, a surprising characteristic in light of the prior art, and the compound demonstrated a superior survival advantage for patients with advanced pancreatic cancer when compared to 5-FU, the previous standard of care. (Green 178:5-15; PTX 436 at 2403.)

Defendants' expert, Dr. Isacoff, testified that gemcitabine is no better than 5-FU in treating patients with advanced pancreatic cancer and that Lilly's findings that gemcitabine presented an improved treatment were based on faulty experimentation. (Isacoff 1433:5-7.) His testimony

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(...continued)
Teva Pharms USA, Inc., 395 F.3d 1364, 1366 (Fed Cir 2005), dealt with an improvement patent application filed eleven years after the earlier patent had issued. By contrast, here, the '614 patent did not issue until 1989, four years after the original application leading to the '826 patent.

is directly refuted, however, by the review of the FDA and the Oncologic Drug Advisory Committee, which approved Lilly's experimental method. (Green 203:8-21; Pearce 115:12-21, 119:8-10). Further undermining his assertion is the fact that the National Comprehensive Cancer Network Guidelines in Oncology determined that gemcitabine monotherapy is the standard of care, whereas 5-FU is merely "salvage therapy." (Green 206:15-207:8, 227:5-10; PTX 480 at MS-14.)[48]

Furthermore, Defendants' contention that gemcitabine does not offer survival benefits and various other surprising properties is unconvincing in light of their admitted desire to market and sell gemcitabine as a pancreatic cancer treatment. The evidence adduced at trial clearly shows that gemcitabine exhibited many surprising and superior characteristics in view of the prior art, which support a finding that the invention would not have been obvious. See Knoll Pharm., 367 F.3d at 1385.

2. Long-Felt Need

Evidence of a long-felt and unsolved need for the solution offered by the patented invention supports a showing of nonobviousness. Tec Air., Inc. v. Denso Mfg. Mich., Inc., 192 F.3d 1353, 1361 (Fed.

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[48] Moreover, it is worth noting that Dr. Isacoff's contention in this regard is belied by his own testimony elsewhere, in which he stated that he prescribes gemcitabine to half of his patients with advanced pancreatic cancer. (Isacoff 1462:13-16.)

Cir. 1999). Based on the previously discussed opinion of Dr. Isacoff that gemcitabine offered little or no improvement over 5-FU, Defendants contend that gemcitabine did not meet any need. Once again, the choice by the National Comprehensive Cancer Network to make gemcitabine, and not 5-FU, the standard of care for the treatment of pancreatic cancer seriously undermines Defendants' position. Although gemcitabine did not present a a cure for pancreatic cancer, it was the first drug in thirty years to produce an improvement in overall survival. (Green 202:7-12; PTX 436 at 2412.) Indeed, gemcitabine remains the standard of care at present and is generally regarded as the most effective drug for the treatment of advanced pancreatic cancer. (Green 179:12-20; PTX 456 at 267-73; PTX 480 at MS-14.) Accordingly, it is clear that gemcitabine met a long-felt need, a finding that lends strong support to the conclusion that the anticancer invention claimed in the '826 patent would not have been obvious.

3. Commercial Success

The commercial success of an invention is evidence of its nonobviousness. Goodyear Tire & Rubber Co. v. Ray-O-Vac Co., 321 U.S. 275, 279 (1944); Al-Site Corp. v. VSI Int'l., Inc., 174 F.3d 1308, 1325-26 (Fed. Cir. 1999). Although the patentee generally bears the burden of establishing a nexus between commercial success and the merits of the patented invention, this nexus is presumed where, as here, "the marketed product embodies the claimed features, and is coextensive with them."

Brown & Williamson, 229 F.3d at 1130 (citing J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997); Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392-93 (Fed. Cir. 1988)); (see PTX 443; Green 217:9-19 (explaining that Gemzar® has been approved solely as an anticancer agent and that gemcitabine is its sole active ingredient).)

Worldwide sales of Gemzar®, the commercial name of gemcitabine, have exceeded $1 billion annually since 2003. (Grabowski Rep. ¶¶ 14, 35, Ex. 2.) The drug has captured over 90 percent of the market of patients with advanced pancreatic cancer, as well as over 50 percent of patients with invasive bladder cancer. Defendants contend that Lilly's marketing expenditures rebut the nexus between commercial success and the benefit of the claimed invention. However, Gemzar®'s ratio of marketing expenditures to sales revenues is not excessive relative to its direct competitors. (Grabowski Rpt. ¶¶ 18, 48, 49, Ex. 6A, 6B.) Moreover, those expenses do not exceed the average ratio for other oncology drugs. (Id.) Accordingly, Lilly's marketing expenditures cannot rebut the nexus between Gemzar®'s benefit and its commercial success.

The trial record makes clear that the singular benefits made available by gemcitabine have led to commercial success, a fact further supported by Defendants' current attempts to market the drug themselves. Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 2001 WL 1397304, at *12 (S.D. Ind. Oct. 29, 2001) ("If the patented drug were not a

commercial success, generic manufacturers would have little interest in offering their own versions of the drug.") "[P]articularly telling" in the case at bar is the fact that Defendants hope to sell Gemzar®, despite already selling a generic version of 5-FU, the former standard of care for pancreatic cancer. (Lee 73:10-11); see Forest Labs., 438 F.Supp.2d at 496. Accordingly, the commercial success of Gemzar® provides additional objective evidence of the nonobviousness of gemcitabine.

4. The Failure of Other Nucleoside Analogs

Evidence that others in the art failed despite concerted efforts to develop inventions similar to the patentee's invention is also recognized as objective evidence of nonobviousness. Knoll, 367 F.3d at 1385. As of the time of the filing of the application in 1984, thousands of nucleoside analogs had been subjected to research and testing, and only one, 5-FU, had been approved by the FDA for use against solid tumors. (Green 179:21-180:5.) Moreover, that single drug had not been approved for the primary utilization of Gemzar®. (Green 179:16-20.) This track record of failure prior to Lilly's success with gemcitabine provides clear support for a finding of nonobviousness.

5. Copying of Gemcitabine

A showing of nonobviousness is also supported by evidence of copying. Diamond Rubber Co. of N.Y. v. Consol. Rubber Tire Co., 220 U.S. 428, 441 (1911). By the year 2000, forty nucleoside analogs had been

reported in the literature imitating the geminal difluoro substitution at the C-2' position found in gemcitabine. (PTX 620 at 87.) This evidence of copying also objectively supports a finding of nonobviousness.

The secondary, objective evidence of nonobviousness adduced at trial - including gemcitabine's unexpected properties, its capacity to fill a long-felt need, its commercial success, similar compounds' failure to demonstrate successful properties, and other researchers' endeavors to copy gemcitabine - reinforces the Court's conclusion that the claimed inventions would not have been obvious.

VI. Enablement

The statutory basis for the enablement requirement is found at 35 U.S.C. § 112, which provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

The "enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999 (Fed. Cir.

2008) (quoting AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003)). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting Ex Parte Jackson, 217 U.S.P.Q. 804, 807 (1982)). Enablement is determined as of the filing date of the patent application. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1988).

The Federal Circuit has explained that "the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." In re Cortright, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (quoting In re Ziegler, 992 F.2d 1197, 1200 (Fed. Cir. 1993)). There is a lack of utility under § 101 "when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." 165 F.3d at 1356 (quoting Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762 (Fed. Cir. 1984)).

With the expert testimony provided by Dr. Kenneth Tew, Defendants contend that the disclosure of the '826 patent does not enable claim 7. According to Dr. Tew, because undue experimentation, in the form of clinical trials, is necessary to determine which tumors would be

susceptible to gemcitabine, claim 7 is not enabled. (Tew 1264:3-9; 1282:15-1283:22.) Dr. Tew testified at length about the extensive work that must be done to design a clinical trial, stating that such a process is "invariably complex" and can cost "tens of millions of dollars." (Tew 1254:23-1256:12, 1261:4-1263:22, 1265:3-1266:2.) Dr. Tew did not, however, cite any references to support many of his assertions, which casts doubt upon those averments. See Upjohn, 225 F.3d at 1311.

Furthermore, the fact that experimentation may be complex does not necessarily make it undue. If the art typically engages in such experimentation, it is not undue, and the enablement requirement is met. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); PPG Indus., 75 F.3d at 1564. Although Dr. Tew is correct in asserting that clinical trials were necessary to determine which neoplasms would be susceptible to gemcitabine, such trials were standard and routine to a person of ordinary skill in the art in 1984. (Green 223:17-25.) During his testimony, Dr. Tew admitted as much. (Tew 1286:6-11 (stating, with regard to the design of clinical trials, "that's what pharmacologists and clinical oncologists do").)

Moreover, as the evidence at trial established, and Dr. Tew admitted, the approach to designing clinical trials is "well documented" in the literature. (Tew 1284:9-25, 1285:1-17.)[49] Where, as here, it

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[49] Besides this admission, the foundations for Dr. Tew's contention regarding the "complexity" of the necessary clinical trials are seriously flawed, in that he treats gemcitabine as though

(continued...)

requires only routine experimentation to determine whether a given embodiment falls within the scope of the claim, it is axiomatic that the claim is enabled. PPG Indus., 75 F.3d at 1564; In re Angstadt, 537 F.2d 498, 504 (C.C.P.A. 1976). Therefore, Defendants have failed to show by clear and convincing evidence that claim 7 of the '826 patent was not enabled.

VII. Conclusion

For all of the reasons explicated above, the Court hereby declares that:

(1) Because Lilly is collaterally estopped from defending against Defendants' claim of obviousness-type double patenting, claim 7 of the '826 patent must be declared invalid on that basis, subject to a final determination of the companion case out of the Eastern District of Michigan now pending before the Federal Circuit.

(2) Defendants have failed to prove by clear and convincing evidence that either

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(...continued)

it were patented for use in all mammals for all types of cancer. This ignores the prosecution of the patent, which clearly demonstrated that gemcitabine was intended for use in humans alone (E.g., Green 220 6-22, 223:11-16, PTX 2 at col. 16, ll. 2-8.)

claim 12 of the '614 patent or claim 7 of the '826 patent is invalid as anticipated under 35 U.S.C. § 102; invalid as obvious under 35 U.S.C. § 103; or invalid for lack of enablement under 35 U.S.C. § 112; and unenforceability due to inequitable conduct has neither been alleged nor proved by Defendants. The asserted claim of the '614 patent is, therefore, neither invalid nor unenforceable.

(3) Defendants stipulated that if the asserted claims of the '614 patent and '826 patent are not invalid or unenforceable, then its actions regarding its gemcitabine products that are the subject of ANDA Nos. 090644, 77-961, and 77-983 constitute infringement of claim 12 of the '614 patent. The Court therefore finds that Defendants have infringed and threatened to infringe in the future claim 12 of the '614 patent.

Accordingly, it is hereby ORDERED THAT:

(1) Pursuant to 35 U.S.C. § 271(E)(4)(A), the effective date of any approval of the gemcitabine products that are the subject of ANDA Nos. 090644, 77-961, and 77-983 SHALL NOT BE a date that is earlier than the latest date of expiration of Lilly's '614 patent.

(2) Pursuant to 35 U.S.C. § 283 and 35 U.S.C. § 271(e)(4)(B), Defendants and their officers, agents, servants, employees, privies, and other acting for, on behalf of, or in concert with them or either of them are PERMANENTLY ENJOINED from the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the gemcitabine products that are the subject of ANDA Nos. 090644, 77-961, and 77-983, or any gemcitabine product that is not colorably different therefrom, prior to the date of expiration of Lilly's '614 patent. This permanent injunction order is effective immediately upon the entry of this ruling. Final judgment shall enter accordingly.

IT IS SO ORDERED.

Date: 03/31/2010

/s Sarah Evans Barker
SARAH EVANS BARKER, JUDGE
United States District Court
Southern District of Indiana

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Appendix D

United States Court of Appeals
for the Federal Circuit

SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Plaintiff-Appellee,

v.

ELI LILLY AND COMPANY,
Defendant-Appellant.

2010-1105

Appeal from the United States District Court for the Eastern District of Michigan in case no. 07-CV-15087, Judge George Caram Steeh.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner LLP, of Reston, Virginia, filed a combined petition for panel rehearing and rehearing en banc for defendant-appellant. He also filed a reply to the brief amici curiae of Teva Parenteral Medicines, Inc., et al. With him on the petition and reply were ROBERT D. BAJEFSKY, HOWARD W. LEVINE, ROBERT F. SHAFFER,

and JESSICA R. UNDERWOOD, of Washington, DC. Of counsel on the petition and reply was JAMES P. LEEDS, Eli Lilly and Company, of Indianapolis, Indiana.

JAMES F. HURST, Winston & Strawn LLP, of Chicago, Illinois, filed a response to the combined petition for plaintiff-appellee. With him on the response were GAIL J. STANDISH and PETER E. PERKOWSKI, of Los Angeles, California.

MATTHEW D. MCGILL, Gibson, Dunn & Crutcher LLP, of Washington, DC, for amicus curiae Washington Legal Foundation. With him on the brief was WILLIAM G. JENKS. Of counsel on the brief were DANIEL J. POPEO and RICHARD A. SAMP, Washington Legal Foundation, of Washington, DC.

LESLIE MORIOKA, White & Case LLP, of New York, New York, for amicus curiae Biotechnology Industry Organization. Of counsel on the brief were HANS SAUER, Biotechnology Industry Organization, of Washington, DC; CHRISTOPHER M. HOLMAN, UMKC School of Law, of Kansas City, Missouri.

DAVID W. OGDEN, Wilmer Cutler Pickering Hale and Dorr LLP, of Washington, DC, for amicus curiae Pharmaceutical Research and Manufacturers of America. With him on the brief were DAVID A. MANSPEIZER, of New York, New York and FELICIA H. ELLSWORTH, of Boston, Massachusetts.

ELIZABETH J. HOLLAND, Kenyon & Kenyon LLP, of New York, New York, for amici curiae Teva Parenteral Medicines, Inc. and Teva Pharmaceuticals USA, Inc. With her on the brief was SHEILA MORTAZAVI.

Before RADER, *Chief Judge*, NEWMAN, LOURIE, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, *Circuit Judges*.

PER CURIAM.

NEWMAN, *Circuit Judge*, with whom RADER, *Chief Judge*, and LOURIE and LINN, *Circuit Judges*, join, dissents from the denial of the petition for rehearing en banc.

ORDER

A combined petition for panel rehearing and rehearing en banc was filed by Defendant-Appellant, and a response thereto was invited by the court and filed by Plaintiff-Appellee. The court granted leave to Defendant-Appellant to file a reply.

The court also granted leave to file briefs amici curiae to Pharmaceutical Research and Manufacturers of America, Biotechnology Industry Organization, Washington Legal Foundation, and Teva Parenteral Medicines, Inc. (f/k/a SICOR Pharmaceuticals, Inc.), et al. Appellant filed a

motion for leave to file a reply to the brief amici curiae filed by Teva Parenteral Medicines, Inc., et al.

The petition for panel rehearing was considered by the panel that heard the appeal, and thereafter the petition for rehearing en banc, response, reply, and briefs amici curiae (and Appellant's reply thereto) were referred to the circuit judges who are authorized to request a poll on whether to rehear the appeal en banc. A poll was requested, taken, and failed.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) Appellant's motion for leave to file a reply to the brief amici curiae submitted by Teva Parenteral Medicines, Inc., et al. is granted.

(2) The petition of Defendant-Appellant for panel rehearing is denied.

(3) The petition of Defendant-Appellant for rehearing en banc is denied.

(4) The mandate of the court will issue on November 8, 2010.

FOR THE COURT

November 1, 2010 /s/ Jan Horbaly

Date

Jan Horbaly
Clerk

cc: James F. Hurst, Esq.
Charles E. Lipsey, Esq.
Leslie Morioka, Esq.
David W. Ogden, Esq.
Elizabeth J. Holland, Esq.
Matthew D. McGill, Esq.

United States; Court of Appeals
for the Federal Circuit

SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Plaintiff-Appellee,

v.

ELI LILLY AND COMPANY,
Defendant-Appellant.

2010-1105

Appeal from the United States District Court for the Eastern District of Michigan in case no. 07-CV-15087, Judge George Caram Steeh.

ON PETITION FOR REHEARING EN BANC

NEWMAN, Circuit Judge, with whom RADER, Chief Judge, and LOURIE and LINN, Circuit Judges, join, dissenting from denial of the Petition for Rehearing En Banc.

I respectfully dissent from the court's denial of the request to rehear this case *en banc*, for inconsistent precedent warrants clarification. Until

recently the law of double patenting was clear, but it has become distorted by divergent statements, leading to this flawed ruling.

Until recently it was beyond dispute that the law of double patenting is concerned only with what is patented—that is, what is claimed. To determine whether there is double patenting it is the claims that are compared; thus, obviousness-type double patenting occurs when the claims of a later patent are an obvious variant of the claims of an earlier patent. The specifications of the patents are irrelevant to the double patenting analysis, other than to guide in construing the claims. A double patenting analysis occurs only when the earlier patent is not prior art against the later patent.

For the patents here at issue, the first application filed on behalf of the Eli Lilly inventors described a new class of chemical compounds having antiviral utility, including the compound named gemcitabine. Thereafter, Lilly filed a continuation-in-part application disclosing but not claiming the anticancer utility of gemcitabine, and on the same day Lilly filed a separate application having a different inventive entity, describing and claiming the use of gemcitabine to treat cancer.[1] The parent

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[1] Lilly explains that the anticancer information was concurrently added to the specification for the compound claims in an abundance of caution concerning the "best mode" of use of these compounds.

specification, but not the continuation-in-part, is prior art against the application claiming the anticancer use.

It has been held that the claims to gemcitabine and its antiviral use do not render obvious the claims to use of gemcitabine to treat cancer, and that the anticancer use claims are patentable over all of the known prior art.[2] This issue is not now before us. However, the panel held the claims to the anticancer use to be invalid for double patenting because the anticancer use was mentioned (but not claimed) in the continuation-in-part specification that is not prior art, stating that "[t]he asserted claims of the later '826 patent simply claim the anticancer use disclosed in the specification of the '614 patent," reported at 611 F.3d at 1389. This is the double patenting ruling for which Lilly seeks review *en banc*.

The law of double patenting is contrary to the panel's holding. In *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1277 (Fed. Cir. 1992), the court stated the established rule that "[d]ouble-patenting is altogether a matter of

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[2] After the district court here entered final judgment, a district court held that the earlier patent disclosing gemcitabine and its antiviral use do not render the anticancer method claims obvious under §103. *See Eli Lilly & Co. v. SicorPharms., Inc.*, 705 F. Supp. 2d 971,1004-10 (S.D. Ind. 2010).

what is claimed." Precedent illustrates this rule in a variety of situations. *See id.* at 1281 ("Our precedent makes clear that the *disclosure* of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, *even where the disclosure is found in the claims.*"); *In re Braat*, 937 F.2d 589, 594 n.5 (Fed. Cir. 1991) ("The patent disclosure must not be used as prior art."); *In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986) ("In considering the question [of obviousness-type double patenting], the patent disclosure may not be used as prior art.").

This law was also fully established in our predecessor court. *E.g.*, *In re Vogel*, 422 F.2d 438, 441 (CCPA 1970) ("In considering the question [of obviousness-type double patenting], the patent disclosure may not be used as prior art."); *In re Plank*, 399 F.2d 241, 242 (CCPA 1968) ("Its claims are used as the basis for a double patenting rejection. It is not a prior art reference."); *In re Aldrich*, 398 F.2d 855, 859 (CCPA 1968) ("[W]e reiterate that double patenting rejections cannot be based on section 103, or on the disclosures of the patents whose claims are relied on to demonstrate double patenting or on the 'disclosures' of their claims."); *In re Boylan*, 392 F.2d 1017, 1018 n.1 (CCPA 1968) ("[I]n analyzing cases of these types, it must always be carefully observed that the appellant's patent is not 'prior art' under either section 102 or section 103 of the 1952 Patent Act. . . ."); *In re Braithwaite*, 379 F.2d 594, 600 n.4 (CCPA 1967) ("While analogous to the non-

obviousness requirement of 35 U.S.C. § 103, that section is not itself involved in double patenting rejections because the patent principally underlying the rejection is not prior art."); *In re Borah*, 354 F.2d 1009, 1018 (CCPA 1966) ("We have no prior art here."); *In re Sutherland*, 347 F.2d 1009, 1015 (CCPA 1965) (stating that claims relied on in double patenting rejections are not treated as prior art); *In re Sarett*, 327 F.2d 1005, 1013 (CCPA 1964) ("We are not here concerned with what one skilled in the art would be aware from reading the claims but with what inventions the claims define.").

Uniformly, unlike examination for obviousness based on prior art, the issue of obviousness-type double patenting is directed to whether the invention claimed in a later patent is an obvious variant of the invention claimed in an earlier patent. The panel opinion violates a vast body of precedent.

The panel apparently was misdirected by an overly-broad statement in *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003). *Geneva* stated that "[o]ur predecessor court recognized that a claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use." *Id.* at 1385-86. The court cites a 1931 decision, *In re Byck*, 48 F.2d 665, 666 (CCPA 1931), in which the court stated:

> It would shock one's sense of justice if an inventor could receive a patent upon a composition of matter, setting out at length in the specification the useful purposes of such composition, manufacture and sell it to the public, and then prevent the public from making any beneficial use of such product by securing patents upon each of the uses to which it may be adapted.

The *Geneva* decision does not mention *Byck*'s further statement that the patentee "might have disclosed a use of the invention which, together with other elements, might have constituted a separate invention for which he would be entitled to a patent. This, we hold, he did not do, in view of the [prior art] Baekeland reference." *Id.* at 667. However, as in this case, there is no "shock" to "one's sense of justice" where the non-obvious, later-claimed use is the result of a later discovery. Yet the statement in *Geneva* took on a life of its own, as in *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, 518 F.3d 1353 (Fed. Cir. 2008), where the court declined to apply section 121 (negating double patenting among divisionals) and found double patenting despite a restriction requirement, citing *Geneva* for authority.

Extending *Geneva* to cover the facts of this case does not further the policy of obviousness-type double patenting. "Obviousness-type double patenting is a judicially created doctrine intended to prevent *improper* timewise extension of the patent

right by prohibiting the issuance of claims in a second patent which are not 'patentably distinct' from the claims of a first patent." *Braat*, 937 F.2d at 592. The panel failed to explain how Lilly's claims to the use of gemcitabine to treat cancer, discovered after gemcitabine's antiviral use was disclosed in the original application, improperly extend the patent right to gemcitabine as a compound, let alone how these claims would "shock one's sense of justice." For purposes of this case, there is no dispute that Lilly would be entitled to a separate patent on the anticancer use if Lilly had not included the disclosure of anticancer use in the specification of the continuation-in-part filed the same day. Such disclosure does not "improperly extend" any patent.

The *amici curiae* explained that particularly for biological/pharmaceutical products, new uses may be discovered as research continues after the initial filing. The Biotechnology Industry Organization explains:

> BIO's members routinely engage in continuing research on basic biotechnology inventions even after initial patent applications have been filed. Often, such research reveals something new about a basic invention, including better and unexpected new ways of using it that require patent protection for their commercial development.

Br. of *Amicus Curiae* in Support of Def.-Appellant Eli Lilly & Co.'s Combined Pet. for Panel Reh'g and Reh'g *En Banc* at 1.

A change of law "in ways that negatively impact the patentability of important later-discovered uses" serves no public purpose in areas in which commercial development requires patent protection. *Id.* If the majority of the court now believes, as a matter of policy, that the law should be changed in this new direction, *en banc* treatment is particularly appropriate, for the court's rule is that the earlier precedent prevails unless overruled *en banc*. A situation in which the court ignores this rule, and applies whatever law the panel prefers, is an indictment of the ability of this court to provide stable law in the areas entrusted to us.

The denial of Eli Lilly's petition for rehearing *en banc* leaves the innovation community without guidance on which the trial courts, and the users of the patent system, can rely. I respectfully dissent.